Justification of the Request for a Negative Vote on ISO DIS 20072 "*Aerosol Drug Delivery Device Design Verification – Requirements and Methods*"

I. INTRODUCTION

This paper has been prepared by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), the European Pharmaceutical Aerosol Group (EPAG) and other experts in response to ISO DIS 20072:2007 *Aerosol Drug Delivery Device Design Verification – Requirements and Methods*. This paper represents the position of the following companies and institutions, all of which have expertise in the design, development, testing, manufacturing or marketing of aerosol drug delivery devices (ADDD) and ADDD-based drug products: 3M, Abbott, Aradigm, Almirall, AstraZeneca, Bespak, Boehringer Ingelheim, Chiesi, Clinical Design, GlaxoSmithKline, Hovione, Lab Pharma, McMaster University, Nektar Therapeutics, Novartis, Novo Nordisk, Pari, Pfizer, PharmaDelivery Solutions, Respironics, sanofi-aventis, Schering-Plough, SkyePharma, Siegfried Inhalation, Teva, Trudell Medical International, Valois, and Vectura. Although much progress has been made during this standard's development by adopting a risk assessment approach, the compromises present in the current ISO DIS 20072:2007 create a standard that is inappropriate for ADDD. The paper therefore justifies the request for casting a negative vote on ISO DIS 20072:2007.

II. RECOMMENDATION

The unanimous recommendation from the entities listed above is to cast a negative vote on ISO DIS 20072:2007. The timing of the standard is premature, the standard does not fulfil its purpose, exceeds its scope and departs from its declared risk-management based approach. It is recommended that the standard be deferred for at least three years before/if restarting the work.

III. KEY PROBLEMS WITH ISO DIS 20072:2007

The current draft standard ISO DIS 20072:2007 is unsuitable as an international standard for ADDD for the following key reasons:

1. The standard's requirements are inconsistent with its stated objective. While the standard claims to be for device design verification, it is built upon verifying a "performance profile" which must involve testing of the drug product. As a result of exceeding its scope, ISO DIS 20072 is attempting to

standardize an area that is already heavily regulated, leading to conflicts with regulatory expectations set by national and international authorities.

2. The standard departs from its declared basis of risk analysis and risk management specific to each product by prescribing the minimum probability content (*p*). Moreover, the values for *p* proposed in ISO DIS 20072:2007 are set so high that meeting the statistical requirements will be challenging or even impossible for many ADDD-based products. One of the unintended consequences of such an approach is that the standard creates barriers to ADDD development around the world. If a risk-assessment approach were to be followed consistently in the standard, the ADDD and drug product developers would be allowed to determine the appropriate combination of probability content, limits and confidence level for a given product based on the risk assessment.
3. Many technical flaws remain in the proposed standard.

A more detailed discussion of each of these issues is presented below.

IV. DISCUSSION OF KEY PROBLEMS

1. The Standard's Requirements Are Inconsistent With Its Stated Purpose

ISO 20072 is meant to be a device design verification standard but due to the nature of ADDD the drug must be involved to confirm device performance. So for many performance tests, it is the drug product rather than the device that is tested. For example, the standard requires testing the aerodynamic particle size distribution (APSD) as part of verifying the performance profile. However, APSD is just as much determined by the drug formulation as by the device. In fact, given the same device, different APSDs could be obtained with different formulations, creating ambiguity when applying this standard.

Furthermore, for many ADDDs, it is impossible to consider the device in isolation from the drug because they are assembled together.

ISO DIS 20072:2007 states that "*This standard intentionally avoids addressing more than the most basic elements regarding the safe and effective use of ADDD in humans. It does not define the pharmaceutical or clinical performance for an ADDD*." These statements seem contradictory to the testing advised by the standard, and are at the heart of a major flaw in this standard. While the standard claims not to define pharmaceutical or clinical performance, it places requirements on emitted mass/delivered dose uniformity (DDU) and APSD **which are recognized as the two most pharmaceutically relevant characteristics of inhalation drug products, not of devices**. Furthemore, the "basic elements regarding safe and effective use of ADDD" are already addressed by numerous other

guidelines for medical devices (e.g., ISO 13485, 21 CFR 820, European Medical Device Directive, *Essential Principles of Safety and Performance of Medical Devices* by the Global Harmonization Task Force, and others).

This proposed ISO standard also ignores the fact that the device design will be verified and validated as part of the drug product authorization as required by national authorities.

As a result of exceeding its scope and placing requirements on the performance of the drug delivered by the device, ISO 20072 is standardizing an area that is already heavily regulated. This in turn leads to conflicts with existing regulatory expectations for these pharmaceutical products set forth by both national and international authorities, such as the US FDA, Health Canada, EMEA, US Pharmacopeia, EU Pharmacopeia, Japanese Pharmacopeia and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). For example, even the *European Medical Device Directive* states that "the monographs of the European Pharmacopoeia notably on (…) interaction between medicinal products and materials used in devices containing such medicinal products" should be regarded as harmonized standards. The ISO draft ignores monographs of the European Pharmacopoeia, which are harmonized standards.

Overall, these inconsistencies with the existing regulatory framework make both the need for and a benefit of an ISO standard for ADDDs doubtful.

2. Statistical Requirements Are Inconsistent with the Risk Management Approach and Are Unreasonably Strict

By prescribing the minimum probability content *p*, and by setting it unusually high, the standard departs from its risk-assessment approach and sets forth such statistical requirements for DDU and APSD that they exceed technical capabilities of ADDD device delivery as demonstrated by many ADDD-based products already on the market or in development.[1]

Even though the draft standard does not prescribe the limits (or a "target interval"), which should rightfully be determined based on the risk assessment and the intended use of a given product, the standard does prescribe the minimum probability content *p* and sets it so high that very broad limits (e.g., broader than 70-130% label claim for delivered dose uniformity) would be needed to pass the test for many current ADDD-based products, while the sample size (i.e., hundreds of inhalers per test) would also have to be much larger than currently used.

[1] The Appendix to this paper contains several data-based illustrations of the strictness of the ISO 20072 requirements as applied to delivered dose uniformity.

Although the tests described in the ISO standard are not intended to be used for routine quality control, and the limits for these ISO tests do not need to match regulatory quality control limits, it is not clear (1) whether regulatory authorities would accept such widely differing limits for the device design verification compared to the limits used for routine release and stability, and (2) how these very broad design verification limits would actually benefit the ultimate users of these products.

Even if the standard added an explicit clarification that the design verification limits do not have to match the regulatory release and stability limits, it is possible that regulatory authorities could mistakenly apply the standard's requirements with their typical limits required for ADDD-based products.

If the risk assessment approach advocated in the standard were to be followed consistently, the ADDD and drug product developers should be allowed to define the appropriate combination of the probability content, limits and confidence level, which together determine the strictness and necessary characteristics of a test to meet specific objectives for a given product.

For APSD testing, special challenges arise due to the fact that APSD (1) is a multivariate response while the parametric test described in the draft standard is applicable only to univariate metrics; (2) practically feasible APSD testing sample sizes are not large enough to use parametric testing as required by ISO 20072, since only a small number (ca 3-6) inhaler tests per analyst per day can be achieved on cascade impactors, and (3) the benefit of increased testing to patients is minimal due to the inherently large variability of the APSD measurement method.[2,3]

Considering the large number of tests, testing conditions and sample sizes needed for each test, the standard's approach implicitly demands a significant investment to manufacture and test a sufficient amount of drug and ADDDs **just for device design verification purposes**, which is in addition to the design verification and product testing required as part of the ADDD product authorization by national authorities. An ISO standard requiring so much testing (not all of which is justifiably necessary) may therefore in effect inhibit development of new ADDD-based products, especially outside the major industrialized countries. We question whether such an outcome fits with the ISO mission.

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[2] See, for example, the following review and references therein : D. Christopher, P. Curry, W. Doub, K. Furnkranz, M. Lavery, K. Lin, S. Lyapustina, J. Mitchell, B. Rogers, H. Strickland, T. Tougas, Y. Tsong, and B. Wyka. *Considerations for the Development and Practice of Cascade Impaction Testing Including a Mass Balance Failure Investigation Tree*. J. Aerosol Medicine, 16 (3): 235-247 (2003).

[3] For example, the following report documents the variability of one of the metrics obtained in an APSD measurement on ADDD-based products: *Initial Assessment of the ITFG/IPAC Aerodynamic Particle Size Distribution Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration*. 2000. Available at http://ipacrs.com/PDFs/Initial_Assess_of_Particle.PDF

3. Many Technical Flaws Remain

In the comments assembled jointly by EPAG and IPAC-RS, about a hundred specific technical challenges were submitted. Examples of technical flaws that make this standard awkward to use in its current form include erroneous definitions, references to other ISO standards and testing requirements.

Despite attempts by experts to make the standard's terminology consistent and accurate, some of the key terms remain ill-defined. For example, the term "medication" fails to distinguish between "active pharmaceutical ingredient" (API) and "formulation" (=API+excipients). This in turn leads to a misleading term "emitted mass", which could be understood to refer either to "delivered dose uniformity" (i.e., the uniformity of API mass emitted per actuation) or to "shot weight" (i.e., the uniformity of the total formulation mass, including excipients, emitted per actuation). Definitions and requirements for primary and secondary packaging are inconsistent with other ISO definitions and common industry usage, as explained in the detailed comments submitted with the ballot form.

The standard references ISO 14253, which is meant for "non-destructive" tests where method variability can be separated from product variability, whereas emitted dose/DDU and APSD testing are both destructive tests, where method variability cannot be separated from product variability. Furthermore, ISO 14253 is concerned with proving conformance of single measurements with respect to specification limits. Furthermore, the standard deviation (SD) of the emitted dose will include both within-ADDD variation and measurement uncertainty, and thus the measurement uncertainty is already automatically accounted for in the test in 6.4.1.

As stated in section 2 above, the standard's proposed parametric test for APSD is technically inappropriate because it applies to univariate metrics (i.e., where the result of a single measurement is a single number) while APSD measurements are multivariate (i.e., the result of a single measurement is a distribution function). Even if some univariate metric were substituted for APSD, the amount of APSD testing needed to allow parametric evaluation would far exceed typical sample sizes used for APSD measurements, which are highly labour intensive and not amenable to high-volume/high-throughout testing. Furthermore, the variability of APSD measurements are known to be high, in large part due to the method variability rather than to the ADDD/drug product variability. This fundamental limitation will make it difficult for APSD results to comply with the required probability content (if any set of appropriate limits is used), and it will also make such an evaluation of little relevance to the product performance because of the inherently high variability due to the APSD measurement method.[2,3]

Overall, it is evident that ISO 20072 has been built on ISO 11608-1,[4] which may not have been the best starting point for an ADDD standard. The scope of ISO 11608-1 is liquid-based pen-injector systems while ISO 20072 relates to a number of aerosolized systems from pressurized metered dose

[4] ISO 11608-1 (2001) Pen-injectors for medical use -- Part 1: Pen-injectors -- Requirements and test methods

inhalers (pMDIs) to dry powder inhalers (DPIs). Tests and conditions are similar for both standards, and while these may be suitable for liquids, other characteristics are more important for the broader range of inhalation products. The test methods are also very different for pens and aerosol devices. Furthermore, technically achievable performance (e.g., precision and variability) is different between these two systems and should be assessed in the context of the device's intended use. Measuring and dispensing liquids to a high degree of precision and accuracy is far easier to achieve than for aerosol-based systems, which by their two-phase nature require generating, delivering and measuring aerosol clouds that may contain billions of individual, micrometer-sized particles dynamically suspended in the air, that are subject to numerous size-dependent removal processes both before and during collection for assay.[5,6] The typical variabilities of the aerosol generation and measurement process are therefore much greater than those for liquid delivery systems, and the performance expectations cannot be easily translated from one system to the other. Most importantly, the relation of in-vitro or device design verification measurements to clinical performance is in many ways not comparable between injectables and inhaled drugs. While the patient's influence on the drug delivery is minimal during liquid injections so that the device plays a major role in the ultimate drug delivery, the impact of the device is more modest for ADDD-based products due to the significant influence of the patient's inhalation technique, disease state and airway geometry on the ultimate deposition of the drug in the respiratory system.

V. CONCLUSIONS

The timing of creating an ISO standard for ADDD is premature. Currently, the regulatory requirements (e.g., from EMEA, Health Canada and FDA) have emphasis on different areas, and the degree of consensus between industry and regulatory agencies vary. It is therefore recommended that the standard be deferred for at least three years before/if restarting the work.

ISO DIS 20072:2007 covers a broad range of inhalation products and devices where a one-size fits-all approach to statistical requirements is not feasible.

The standard requirements are so extensive (due to both a large number of complicated tests and the challenging statistical requirements which are beyond technical capabilities of many ADDD), that it would effectively limit future ADDD development around the world, make it prohibitive for smaller firms to develop and manufacture ADDDs and ADDD-based products, and would delay or prevent new therapies from reaching patients.

[5] Warren H. Finlay The Mechanics of Inhaled Pharmaceutical Aerosols: An Introduction. Academic Press, San Diego, CA. 2001.

[6] William C. Hinds. Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles. 2nd edition. John Wiley & Sons, Inc. New York, NY. 1999.

ISO DIS 20072 does not fulfil its purpose, exceeds its scope and departs from its declared risk-management based approach. Therefore it should not be supported in its current form.

Appendix

Technical Illustrations, Table and Figures

For the DDU comparisons in Figures 1 and 3 of this Appendix, the limits of 100±20% label claim are used for discussion purposes because they are in line with the current US FDA expectations for ADDD-based products.

Figure 1 presents operating characteristic (OC) curves for the ISO test with different sample sizes. It shows that it is not possible to comply with the ISO requirement with 100±20% limits with an RSD>9% (assuming the batch mean on target, or 100% label claim; these requirements get stricter if the mean is not on target, i.e. for off-target batches, or when a test is performed on a stressed product). Yet, for most ADDD-based products, an RSD of 9% is not uncommon, as documented in the "Initial Assessment of the ITFG/IPAC Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration" (2000, http://ipacrs.com/dose_uniformity.html), which involved 60 ADDD-based products in the main analysis. A relevant portion of the summary data from that report is presented in Table 1 below.

Figure 2 explores the consequences of different limits and demonstrates that very wide limits may be needed to pass the test in ISO DIS 20072:2007.

Figure 3 shows that the requirements of this ISO standard exceed performance capabilities of many ADDD-based products, based on the data from 80 products around the world already on the market or in development.

In stressed conditions, the ADDD variability will likely increase from that illustrated here, and complying with the ISO test requirements will be even more difficult. The standard's lowering of the minimal required probability content from 97.5% to 95% (in stressed conditions) is not nearly enough to provide relief. The correct approach would be to allow ADDD and drug product developers to determine the appropriate combination of the probability content, limits, and confidence level based on a risk assessment for a given product.

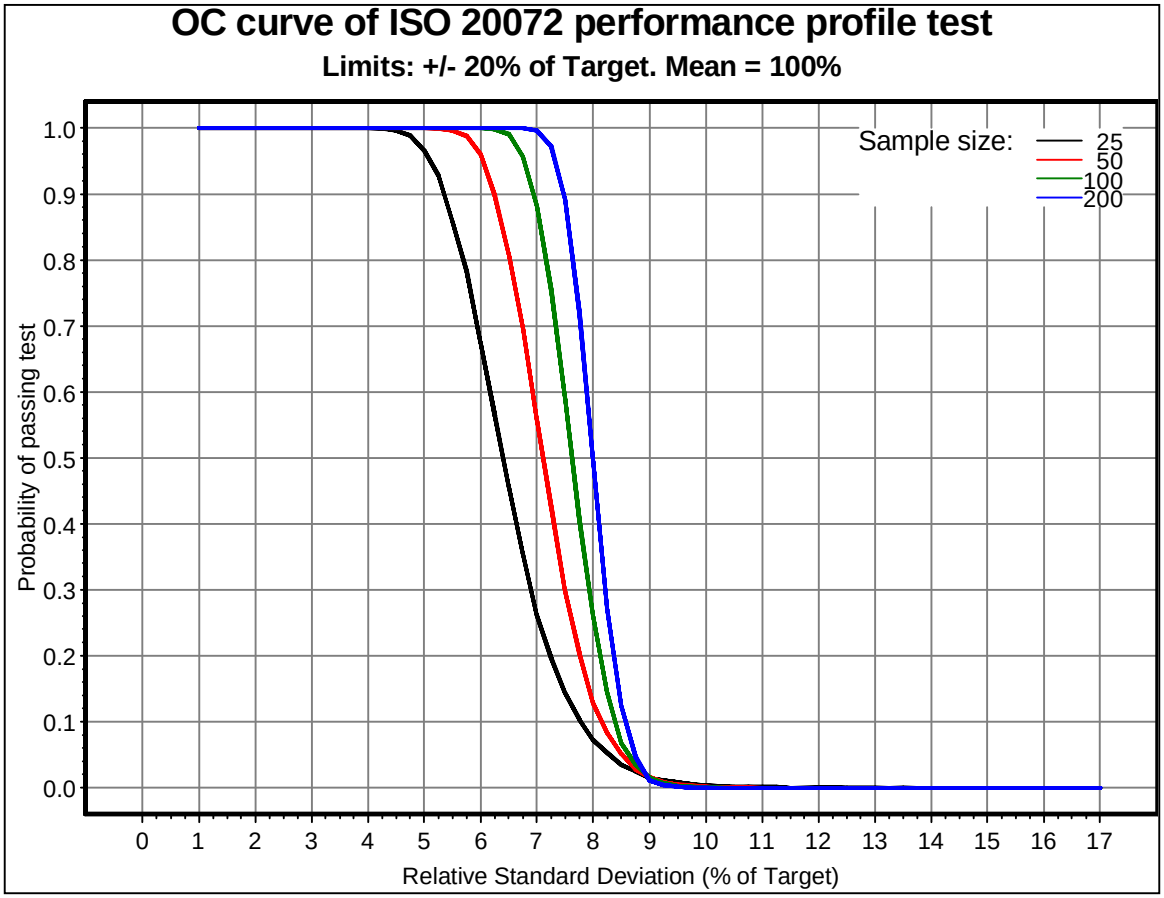

Figure 1. Operating Characteristic (OC) Curves of the Performance Profile Test in ISO DIS 20072:2007 (for different sample sizes). (p=0.975)

This figure plots probability of passing the ISO DIS 20072 test as a function of the batch relative standard deviation (RSD), for a mean on target (100% label claim) and sample sizes 25-200.

For off-target batches, the requirements will be stricter (i.e., the probability of passing lower).

The graph illustrates that products with RSD above about 8% have very low probability of passing the test. For products with RSD above 9%, the probability of passing approaches zero. Yet, it is not uncommon for ADDD-based products to have variabilities in this range. This is illustrated by the data in the ITFG/IPAC database for dose content uniformity (2000), as shown in the table below.

Table 1 (copied from the "Initial Assessment of the ITFG/IPAC Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration" (2000)). The total number of ADDD-based products in that analysis was 60.

Product status (as of 2000)	***RSD %***		
	Mean	***Median***	***Range***
US commercial	6.9	6.8	5.8-8.3
Non-US commercial	9.6	9.3	5.3-16.7
Phase IIB / III / NDA	9.1	8.7	3.5-18.1
Not Disclosed	11.4	*	11.1-11.6
All	9.1	8.6	3.5-18.1

* not meaningful as n=2

Notes:

1. In the 2000 ITFG/IPAC Initial Assessment, the majority of the US commercial products were CFC-based MDIs which have now been phased out and replaced with HFA MDIs, which typically have higher variabilities.

2. In the 2000 ITFG/IPAC Initial Assessment, only fixed-dose products were considered. For variable-dose products, relative variability will increase as the dose decreases due to the absolute precision in dosing mechanisms and measurement systems.

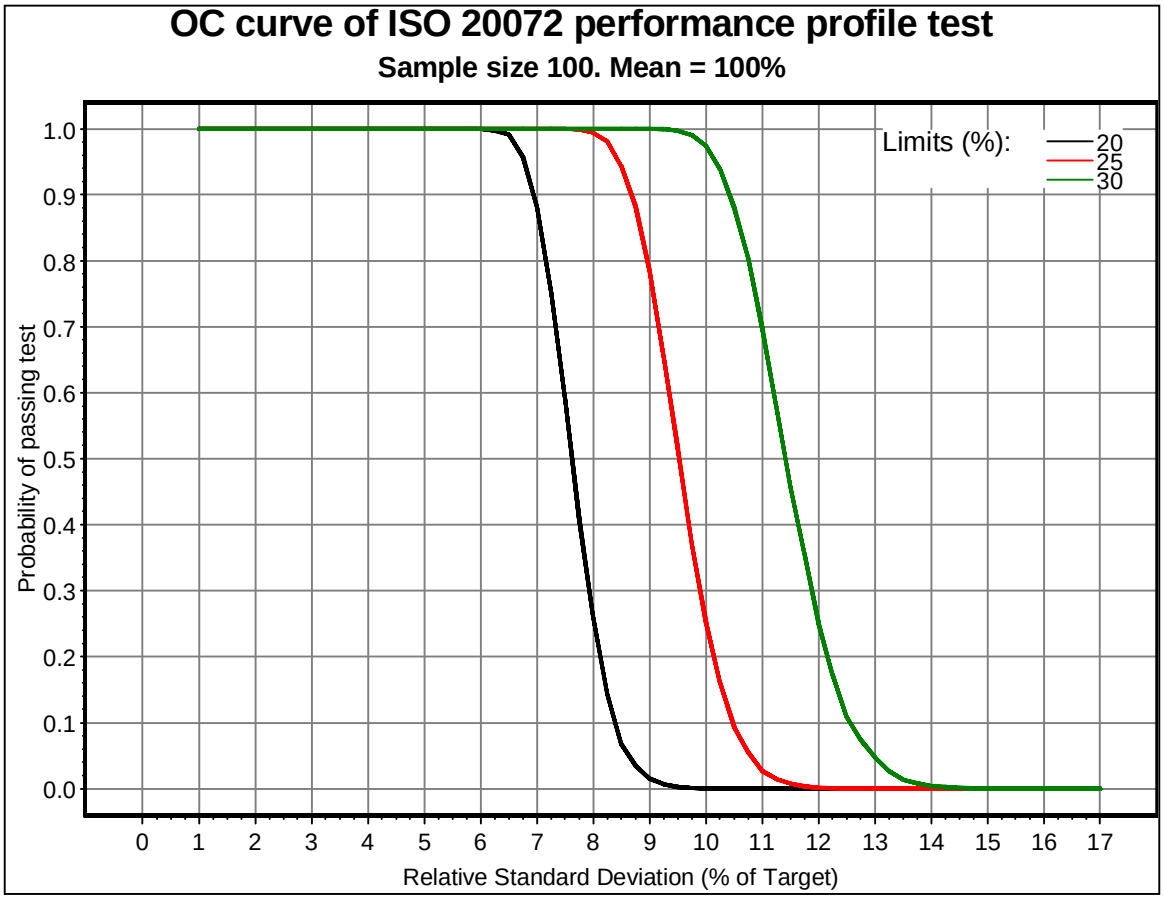

Figure 2. Operating Characteristic Curves of the Performance Profile Test in ISO DIS 20072:2007 (for different target intervals). (*p*=0.975)

Figure 2 shows the probability of passing the ISO DIS 20072:2007 test as a function of the batch RSD for a mean on target and the limits of 100±20, 25 and 30% label claim.

Admittedly, ISO DIS 20072:2007 does not specify the target interval for performance profile testing but rather leaves it to the developer's risk analysis. However, in order to pass, for example the DDU test, very wide limits may be needed (e.g., more 100±30% label claim), as demonstrated in Figure 2 (since for ADDD-based products, variabilities around 10% are not uncommon). This raises the question of the meaningfulness of such limits, such testing and such ISO requirements.

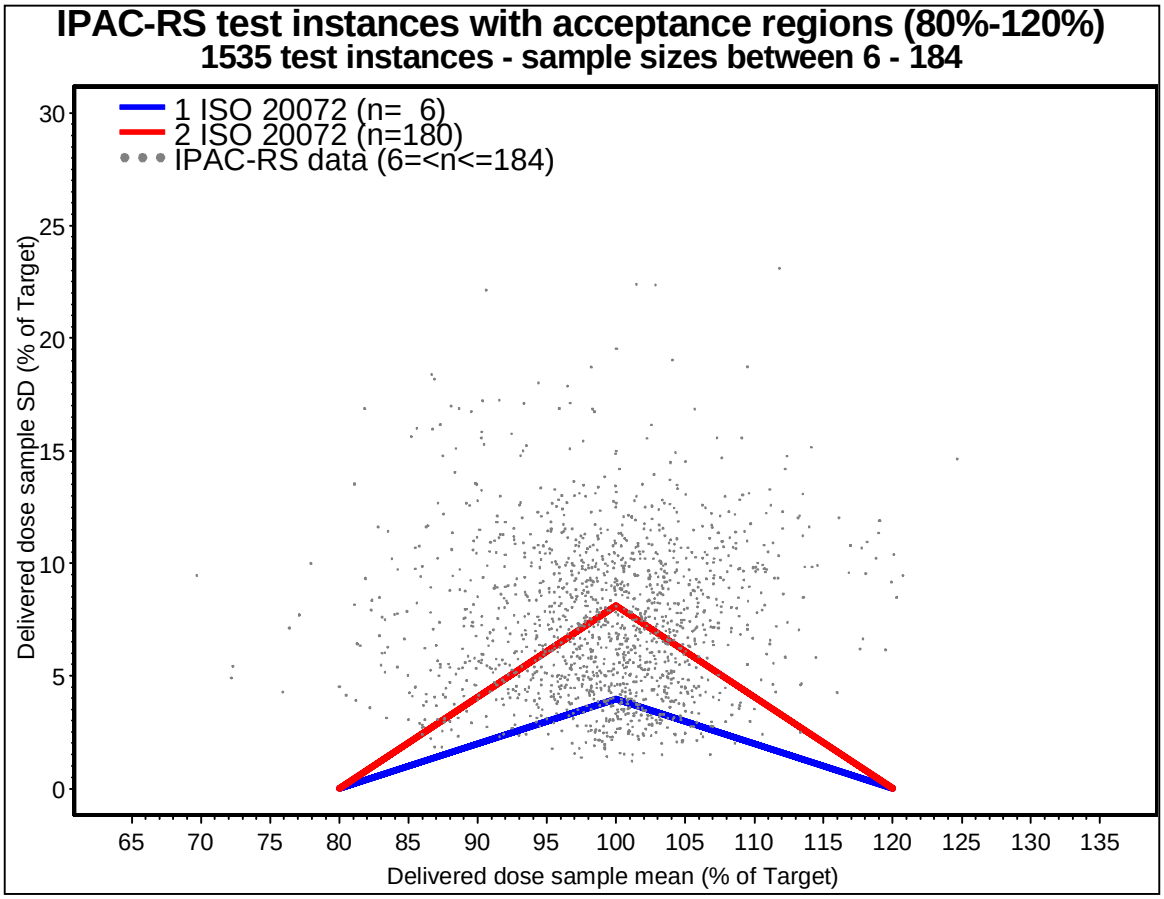

Figure 3. Sample Mean and Sample Standard Deviation of 80 ADDD-based Drug Products in the IPAC-RS DDU Database (2004), compared to the ISO DIS 20072 requirements with sample sizes 6 and 180 (p=0.975) and the FDA-recommended target interval of 80-120% label claim.

The considerations above are further substantiated by the comparison of DDU performance of 80 commercial and late-development ADDD drug products in the IPAC-RS world-wide database (2004) to the requirements of the ISO standard, as illustrated in Figure 3. The ISO requirements clearly exceed the DDU technical capabilities of the majority of ADDD-based products. In addition, for many products, it would require sample sizes larger than those currently accepted, in order to pass the test.