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Use of a Quality-by-Design approach to justify removal of the HPLC weight % assay from routine API stability testing protocols

Peter J. Skrdla*, Tao Wang, Vincent Antonucci, Thomas Dowling, Zhihong Ge, Dean Ellison, John Curran, Ganapathy Mohan, Jean Wyvratt

Merck & Co., Inc., P.O. Box 2000, 126 East Lincoln Avenue, RY818-B205, Rahway, NJ 07065, USA

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ABSTRACT

Due to the high method variability (typically ≥0.5%, based on a literature survey and internal Merck experience) encountered in the HPLC weight percent (%) assays of various active pharmaceutical ingredients (APIs), it is proposed that the routine use of the test in stability studies should be discouraged on the basis that it is frequently not sufficiently precise to yield results that are stability-indicating. The high method variability of HPLC weight % methods is not consistent with the current ICH practice of reporting impurities/degradation products down to the 0.05% level, and it can lead to erroneous out-of-specification (OOS) results that are due to experimental error and are not attributable to API degradation. For the vast majority of cases, the HPLC impurity profile provides much better (earlier and more sensitive) detection of low-level degradation products. Based on these observations, a Quality-by-Design (QbD) approach is proposed to phase out the HPLC weight % assay from routine API stability testing protocols.

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1. Introduction

The Quality-by-Design (QbD) approach put forth by the FDA in 2006 has been increasingly utilized across the industry in various applications, some of which can be found in the recent literature [e.g., 1,2]. In this work, a specific application of QbD is discussed whereby it is proposed that the HPLC weight % assay for the routine stability testing of active pharmaceutical ingredients (APIs; also commonly referred to as “drug substances”) should be eliminated for the majority of compounds in development because the assay results are simply not stability-indicating, to the degree required for most such studies to be meaningful (i.e., following ICH guidelines for the reporting of organic impurities), due to the large assay variability associated with them. Under the QbD paradigm, low-value work is eliminated in favor of efficiently acquiring data in a knowledge-driven manner, followed by the routine monitoring of only those attributes that are critical to demonstrating that a given API has an acceptable and predictable quality profile over its shelf life.

Various works have recently been published that discuss the variability associated with different API HPLC weight % assay methods. For example, Ermer et al. [3] used 44 different APIs and drug products of various kinds (manufactured by many different large pharmaceutical companies), subjected to 156 different stability studies, to obtain a total of 2915 assay values for their HPLC assay precision determination. The intermediate precision, which includes method repeatability in the presence of additional variability caused by differences in reference standards, operators, equipments, reagents, etc., was found to be as high as 1.1% for the drug substances investigated in that work. Görög [4] reported the range of analytical error associated with API HPLC assay methods as “certainly above 0.5% and . . . probably around 1%”. It is highlighted here that Table 2.2.46-1 in the European Pharmacopoeia (Ph. Eur.) lists the repeatability requirements (maximum permitted relative standard deviation, RSD) for replicate injections based on various API limits (98.0–102.0%, 97.0–103.0%, etc.). For example, for an assay specification limit of 97.0–103.0%, the permitted RSD is 1.10% for five replicate injections.

Dejaegher et al. [5] supported the fact that API HPLC assays typically have poor precision (>0.5% RSD) when compared to titration assays (∼ 0.1–0.5% RSD). Their statistical analysis of their own data sets pointed to the use of increased sample/standard weights (>160 mg, versus ≤32 mg for typical assay methods) as a means of lowering the HPLC assay variability down to levels more typical of titration methods. However, in light of this finding one must consider two points: firstly, the larger sample quantities recommended by Dejaegher et al. might not be readily available for stability testing during the early development of an API; secondly, most GMP analytical balances are calibrated to a precision of ±0.03 mg using a 10.00 mg standardized weight at Merck [6] (note: for an assay target weight of 25 mg for both samples and standards, that corresponds to only ±0.1% error), suggesting that analyst

* Corresponding author. Tel.: +1 732 594 2491; fax: +1 732 594 2491.
E-mail address: peter_skrdla@merck.com (P.J. Skrdla).

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error during weighing/sample transfer and not the target mass (alone) is the larger source of error. Of course, none of the literature referenced in this paper advocates the use of a titration method over an HPLC assay method, mainly due to the lack of specificity of the former. Note that due to this lack of specificity, the accuracy of titrimetric and spectrophotometric (e.g., UV–vis) methods can be expected to be poor in the presence of chemically related (e.g., process/degradation product) impurities [4].

Görög [4] published a paper approximately 4 years ago whose basic premise was to cast reasonable doubt on the current industry practice of spending considerable resources to develop and validate specific HPLC assays for various APIs (with respect to the regulatory requirements put forth by the FDA and EMEA), due to the significant analytical variability that is typically encountered when using these methods. Simply put, Görög stated that the characterization of bulk drug materials using these highly specific HPLC methods is "at least questionable" with regard to the high method variability. Note that the high variability has a direct correlation with the relatively wide acceptance criteria, mentioned above.

In a more recent paper [7], workers from Lilly investigated the claims of Görög by studying the assay variability and OOS frequency originating from various API methods, using a database of APIs manufactured at their own company. Extracting a mean variability of 0.6% RSD for these methods, Hofer et al. [7] showed the conclusions of Görög to be generally valid. They proposed the use of a "mass balance accounting" procedure for calculating API potency as a sensible alternative to the HPLC weight % assay (for both API stability and batch release scenarios), in order to minimize overall error and, consequently, to reduce the probability of OOS results that are not API quality driven. It should be noted that Görög originally advocated replacing non-selective and, later, selective assay methods for bulk APIs by the mass balance procedure (discussed more below) [4,8].

Generally, Hofer et al. envisioned that the implementation of HPLC assay methods would pertain only to cases where GMP standards are poor and, thus, gross contamination (not detectable by the HPLC impurity profile method) might occur. Additionally, these workers discussed that HPLC weight % assay methods might have some value during the early development of APIs, where the synthetic processes are still not completely defined. Alternatively, for unstable compounds where the degradation products are not observable in the HPLC impurity profile, the weight % assay might also have some merit (note, however, that this case must be considered in terms of the ICH guidelines for reporting degradation products, which is discussed more later). However, for the vast majority of cases, Hofer et al. support a mass-balance approach, i.e., using the equation: "mass balance = 100 − related compounds by HPLC area% − solvents by GC − water by KF − residue on ignition (ROI)", as a much more sensitive indicator of API quality than the HPLC weight % assay. They went on to state that for well-controlled processes (along the lines of QbD), a tight acceptance criterion for HPLC assays might be "an unnecessary burden on quality control laboratories that does not add value to the quality assessment of the drug substance".

2. Discussion

2.1. Proposal

The target of this proposal is the removal of HPLC weight-based assays from the routine stability testing protocols of most APIs (see the next section for a discussion of possible exceptions), but not the removal of weight-based methods from the list of regulatory tests used for API batch release (although it might be a strategy to consider for late-stage development, e.g., Worldwide Marketing Application/WMA filing and post-approval applications, utilizing QbD considerations). Görög is more liberal in his view of removing weight-based assays beyond the realm of stability testing, suggesting that both specific (e.g., HPLC) and non-specific (e.g., titration and photometric) methods could be generally omitted from analytical testing protocols without endangering the safety of patients [8]. Furthermore, he has advocated the use of multiple purity tests (e.g., using HPLC, TLC and CE) and the use of more sensitive and selective detectors (e.g., MS) to identify impurities that can subsequently be specified, individually (and by name), in the various pharmacopoeias, as an alternative to the more traditional assay methods (with typically quite loose acceptance criteria, e.g., 98.0–102.0%). Not only does the approach of Görög better control API purity (and, consequently, drug safety) than the use of various weight-based assays, it might also point to a good risk mitigation strategy for the current proposal; i.e., by performing a thorough/rigorous method validation of a given impurity profile method, it becomes highly unlikely that the HPLC weight % assay would add value to a given stability testing protocol, even early in development (discussed more later).

For the release of GMP batches, particularly those early in development, a battery of analytical tests is typically performed in an attempt to fully characterize the material. This testing typically includes a weight-based assay of some kind for the API, which, most often, is used simply to confirm (only crudely, because of high method variability) the "mass balance" results obtained by other, more precise, orthogonal determinations (e.g., HPLC area % impurity profile, residual solvents by GC, water by KF and ROI). However, for the routine stability testing of the vast majority of compounds, including those in both early- and late-stage development (that have already passed the scrutiny of extensive release criteria for GMP release), the assay is of much lower value. Primarily, that is the case because ICH guidelines require reporting of impurities/degradation products down to the 0.05% level. Such low levels of impurities can only be accurately detected/monitored using a more precise HPLC impurity profile method (that is not affected by analyst precision during sample/standard preparation), not by an HPLC weight % assay method having an inherent variability of ≥0.5% (which is higher by an order of magnitude than the ICH impurity reporting threshold). For late-stage compounds, as either the acceptable stability profile of the material has already been demonstrated for a given container/storage condition or its degradation mechanism has become fully elucidated in earlier studies and subsequently controlled (e.g., by a change in the packaging or the sample environment), the HPLC weight % assay has even less merit. For the above reasons, it is recommended here that the HPLC weight % assay should not be performed as a routine test to evaluate API stability characteristics. Note that while the use of the "mass balance accounting" approach of Görög [4,8] and Hofer et al. [7] generates a more reliable "assay" result than the HPLC weight % assay for the reasons outlined in this paper, it does not provide any additional stability-indicating information that is not already obtainable from the individual KF and HPLC impurity profile test methods that are typically present in most stability protocols. Therefore, in the authors' opinion, the use of this approach as an alternative to the HPLC weight % test during routine API stability testing does not add value.

2.2. Suggested actions

The authors feel that the ICH guidelines, as well as the pharmacopoeias that often consider them, are "living" documents that need to be updated periodically as technology/understanding evolves/improves (e.g., previous TLC, titrimetric and spectrophotometric methods are increasingly being updated by HPLC-based tests, in the most current editions of the USP and Ph. Eur. [2]). Based on the current understanding of the capabilities and limitations of

the HPLC weight % assay test, as outlined in this manuscript, certain actions are recommended. Firstly, the HPLC weight % assay method (or suitable alternate assay method) should be implemented routinely only at the end-of-study (EOS) time point for the *first* API lot to be put on stability station, for a particular program. The assay result obtained at EOS should be compared both to the assay result at batch release and the API potency calculated at EOS from stability test results, as an approximate (i.e., crude) indicator of mass balance (naturally, a sufficient number of replicates of sample and standard preparations should be injected onto the HPLC column to meet the previously stated, "typical RSD requirement" of 0.5–1.0%). Agreement of these results indicates that the HPLC impurity profile and KF tests, performed at each stability time point, are appropriate control methods, and as a result, the HPLC weight % assay test can be removed from future stability protocols (per the QbD framework). Lack of agreement of these results indicates that the HPLC weight % assay should be retained at the EOS in stability protocols as an analytical tool to assess the API behavior, until such time that mass balance in results is obtained (e.g., using improved methods that better monitor the degradation, or developing a more stable API form). Naturally, exceptions to these recommendations can and should be implemented based on the sound scientific judgment of the process chemists/engineers and analysts involved on a given program, with respect to the chemical stability challenges presented by a particular compound and the limitations of the various analytical methods that might exist for the accurate and precise characterization of that drug substance (e.g., when dealing with non-chromophoric APIs/impurities/degradation products; other scenarios can potentially be identified in future works).

3. Conclusion

The main driver for the proposal is a scientific one; simply put, since the HPLC weight % assay is insensitive to the small changes necessary to monitor API degradation, it is of limited use in this application (in the vast majority of cases). As mentioned earlier, the large error associated with the technique can lead to unnecessary work through "false OOS result" investigations and the over-interpretation of limited data sets in an attempt to identify decomposition trends early during development, not to mention the unnecessary expenditure of time, energy and money in performing the low-value work in the first place [8]. The authors firmly believe that any variation in HPLC weight % assay values observed as a function of storage time are more likely to be a measure of the method variability (e.g., analyst weighing technique) than to be indicative of a real change in API quality. Any real change in quality is more likely to be detected using more precise methods, such as the HPLC impurity profile and KF titration methods, which serve as key control tests in the majority of stability testing protocols. Proper validation of the impurity profile method (e.g., using multiple/orthogonal methods and/or detectors, as discussed by Görög [8]) might serve as a good risk mitigation strategy for the removal of the HPLC weight % assay from such protocols.

4. Future directions

Merck is actively considering opportunities to pilot the proposed QbD-based strategy discussed in this paper by applying it to stability programs currently in development. Furthermore, it is possible to conceive that, along the lines of this proposal, other tests can/should be phased-out or eliminated from API stability protocols under the QbD paradigm, provided that there is sufficient data to demonstrate that their continued routine surveillance does not provide any additional critical information regarding the API stability in its given container/closure system. Furthermore, the authors feel that it might be worthwhile to investigate the applicability of the current proposal to the characterization of drug products upon storage, as many of the principles advanced in this manuscript appear to be similarly relevant. The authors hope that this paper serves to stimulate productive discussions on the "QbD of analytical methods for stability testing" across the industry and with regulatory agencies.

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