Obscuring the message: A critical examination of laboratory test methods for orally inhaled products that could lead the user astray: Part 2—Total Emitted Mass (TEM) and related metrics

This is the second in a two-part educational series discussing potential pitfalls in testing OIPs and ways to avoid them. The first article focused on aerodynamic particle size distribution (APSD) determination and this article discusses total emitted mass.

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Introduction

This article is the second in a two-part series in which laboratory test procedures for the assessment of OIP performance are appraised. This first article focused on determination of aerodynamic particle size distribution (APSD). Attention is now turned towards the determination of the total emitted mass (TEM) of active pharmaceutical ingredient (API), which is the other major *in vitro* performance metric that is identified in the pharmacopeial literature.[1-4] Total mass is often expressed per actuation for pressurized metered dose inhalers (pMDIs) and their associated add-on devices, such as spacers or valved holding chambers (VHCs), as well as for the new soft mist inhalers (SMIs). In the case of dry powder inhalers (DPIs), this metric is expressed per inhalation since the device cannot be operated properly without creating an inspiratory maneuver. In the case of nebulizing systems, however, the situation is more complicated because they are intended to deliver medication either continuously or during inhalation only, in connection with therapy which typically lasts for several minutes. Nevertheless, for the purpose of this article, TEM for nebulizing systems is conveniently considered to be the total mass of API delivered within the treatment time, $t_{treatment,}$ and its adjunct measure of medication delivery rate is simply TEM/$t_{treatment,}$ often expressed in units of μg API/min.

As in Part 1, the focus of the article is to identify potential pitfalls in set-up, execution and analysis that could obscure the findings, and therefore the interpretation of data, that are derived from such measurements. Like its predecessor, this article provides guidance for the selection of the most suitable methods, identifying their limitations and associated potential pitfalls.

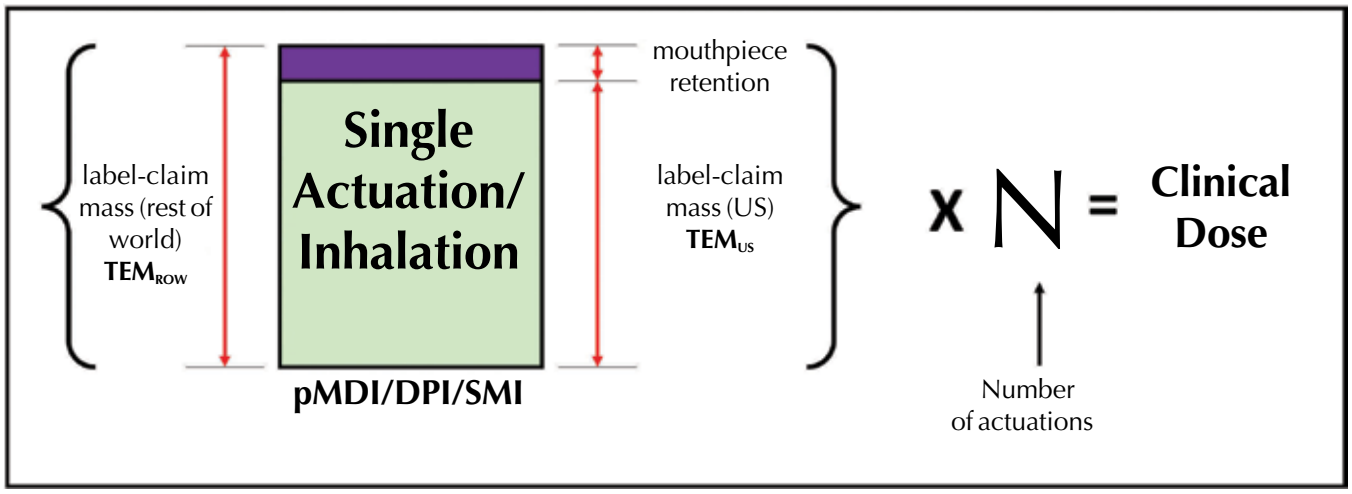
Confusion between total dose and total mass per actuation/inhalation

At the outset, it is important to clarify a commonly encountered misnomer, namely that TEM equates with the total clinically prescribed dose. In the context of OIP testing, the term "dose" should always be understood in terms of its use by the clinical professional, since more than one use (e.g., per actuation of pMDI or SMI, or per inhalation for a DPI), may be required to give the prescribed dose (total dose). On the other hand, the registered label claim "dose" is the mass(es) of API(s) that the manufacturer of the product intends the inhaler to deliver per single actuation/inhalation. The registered label claim "dose" most closely relates to TEM, as measured using a compendial method. In this article, the descriptor "emitted" has been intentionally added to emphasize the difference between the label claim value and the total mass of API that reaches the sampling/measurement apparatus. The relationships between these terms are summarized in Figure 1.

The situation just described is complicated by the fact that, in the US, the FDA requires the registered label-claim "dose" (TEM_{US}) to be expressed ex-mouthpiece, whereas in the rest of the world, this quantity (TEM_{ROW}) relates to the total mass of medication emitted from the inhaler, including that which deposits on the mouthpiece. For the purpose of this article, TEM from here on refers to the rest of world definition. These differences in definitions were captured by the European Pharmaceutical Aerosol Group (EPAG) in a publication presented a few years ago, in which they attempted to identify and standardize the numerous terms and definitions that currently exist in connection with OIPs.[5] In their article, they also referred to emitted dose. However, the

Figure 1

Relationships between the various terms used to describe the total mass of medication delivered from OIPs



prefix "total" has been added in the present article in order to distinguish more clearly these measures from the sub-fractions of the emitted mass that may be related to regional deposition in the respiratory tract.

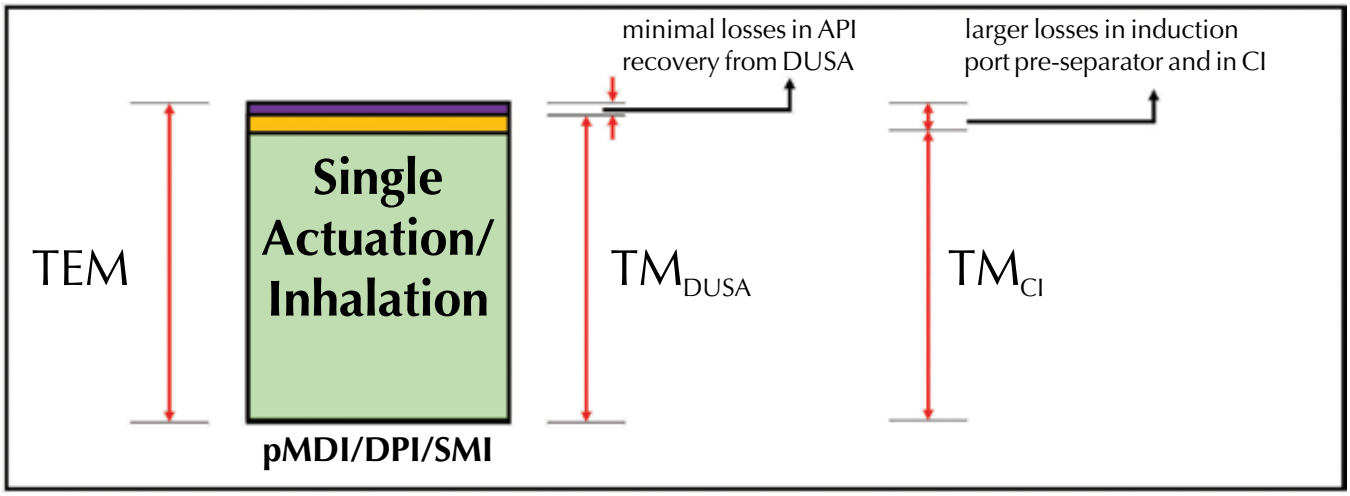
TEM is deemed a critical quality attribute, in addition to APSD, by the regulatory agencies in North America, Europe[6-8] and, indeed, globally. The methods by which both metrics are obtained are well-defined for pMDI, DPI and SMI products in both the US (USP) and European (PhEur) Pharmacopeias.[1,2] Likewise, similar information is provided for nebulizing systems in both pharmacopeias; in addition, guidance is provided for the determination of TEM/$t_{treatment}$.[3,4] Although they are not "single actuation/inhalation" in use, nebulizing systems are included with pMDI and DPI products in the considerations that follow, because they deliver a measurable mass of API in a given time interval that can be equated with TEM, when determined from onset of operation to the end of delivery.

Be wary of confusing TEM obtained by the dosage unit sampling apparatus (TM_{DUSA}) with total mass sampled by the cascade impactor system (TM_{CI}) in connection with APSD determination

At first sight, TEM obtained by dosage unit sampling apparatus (TM_{DUSA}) associated with determination of content uniformity, and total mass sampled by the cascade impactor system (TM_{CI}), linked with determination of APSD, should be equivalent, since both metrics essentially describe the total amount of medication emitted from the inhaler-on-test (pMDI or DPI). However, TM_{DUSA} is typically determined after the minimum number of actuations/inhalations usually equivalent to the label-claim dose have been delivered to the sampling apparatus.[1,2] This may be as few as a single actuation/inhalation, depending upon the product involved. In contrast, the number of actuations/inhalations required for a typical APSD determination may be as many as five or ten, depending upon the detectability of the compound and potency of the API. Highly potent substances, such as formoterol fumarate, will require more actuations/inhalations to achieve adequate analytical sensitivity, compared with a relatively low potent API, such as albuterol. The current General Chapter <601> of the US Pharmacopeia specifies that the number of minimum recommended doses (actuations/inhalations) discharged must be sufficient to ensure an accurate and precise determination of APSD, but adds the rider that the minimum number be not greater than ten.[1] The increased number of actuations/inhalations is necessary because the aerosol bolus is fractionated into as many as ten or more components, depending on the measurement apparatus configuration. After recovery, the assay for the pertinent API may therefore result in values close to the limit of detection for some stages. The determination of APSD is also associated with bias from wall deposition within the cascade impactor that can be as much as 5% of TM_{CI}.[1,2] Further reductions in TM_{CI} may also be caused by losses associated with imperfect recovery from the non-sizing components, such as the induction port and pre-separator (if present), as well as the stages and back-up filter (micro-orifice collector in the Next Generation Impactor) (Figure 2). Returning to the determination of TM_{DUSA}, recovery of API from the much simpler apparatus only necessitates assay of one sample per determination, excluding API mass that might be recovered from the mouthpiece of the inhaler itself. It follows that TM_{DUSA} is inherently more sensitive than TM_{CI} to minor variations in API mass from one actuation/inhalation to the next. An important advantage of TM_{DUSA}-based data is that these measurements are likely to be more sensitive to fluctuations in API output through the life of the inhaler, either in use or in storage-based stability trials. Given these differences in methodologies, the normal expectation is that TM_{CI} will be slightly less than TM_{DUSA}.

Figure 2

Relationships between total emitted mass (TEM) and total mass (TM), determined by dosage unit sampling apparatus (TM_{DUSA}) and by cascade impactor (TM_{CI})



In summary, the end use for the data should be the determining factor in deciding whether measurements involving TM_{DUSA} and/or TM_{CI} are required. Furthermore, in the context of a cascade-impactor-based determination undertaken for the purpose of evaluating APSD, TEM (Figure 2) represents the mass balance of the determination, which is regarded by the FDA as a primary measure defining the validity of the measurement, and therefore specified as being between 85% and 115% of the label claim mass per actuation/inhalation.[6]

Be clear about the purpose of testing before designing and undertaking laboratory-based studies

The methodologies for TEM that are provided in the pharmacopeias are primarily intended for use in connection with product quality assessment, as required by the regulatory agencies.[6-8] They are utilized on a product-by-product basis for registration with the regulatory authority and in subsequent quality control related to batch release in production. A key attribute is therefore method simplicity, because the objective is to avoid introducing measurement apparatus bias and imprecision, as far as is possible.[9] Sacrifices are therefore made in terms of attempts to mimic actual patient use.[9] More clinically appropriate methodologies have been developed in recent years, involving the use of breathing simulators, initially providing standardized flow-time patterns mimicking tidal breathing,[10-12] and more recently replaying patient-recorded breathing so that the effect of disease state as well as patient age can be more effectively investigated.[13-14] In conjunction with breath simulation, anatomically appropriate upper airways have been developed as simple-to-manufacture inlets, either modeled on live patient imaging[15-16] or possessing age-appropriate idealized geometries that capture information from many patients.[17-19] Given these advances, it is questionable whether the right-angle bend of the USP/PhEur induction port is appropriate as an entry when attempting to simulate patient use. Such a practice has been commonplace, for example, in the evaluation of pMDI-spacer/valved holding chamber (VHC) performance,[20] and in the course of determining nebulizer-emitted droplet, APSD-based metrics, such as fine droplet fraction, either directly by cascade impactor,[21] or in support of parallel studies to evaluate TEM by filter collection.[22, 23] The Nephele mixing inlet[24] and the ability to interface with a breathing simulator seem to offer closer approximations to clinical reality in terms of predicting lung deposition.[25] In this measurement apparatus configuration, the inhaler experiences inhalation waveforms while still connected to the aerosol measurement device (a filter for TEM or cascade impactor for TM_{CI} and APSD metrics).

Realistic facemask application

Many OIPs, particularly those associated with spacers or VHCs intended for use with medication for older children or adults have a mouthpiece as the patient interface. However, an appropriately sized facemask is necessary for effective medication delivery to infants, small children and adults who are unable to use a mouthpiece.[26] In recent years, much work has been done to devise ways to effectively evaluate OIP/facemask combinations in the laboratory. Early models manufactured from materials that provided rigid facial surfaces[15, 27] did not allow the volume or shape of the dead-space between the exit of the OIP and the face to be realized because the soft facial tissues move in response to force when the facemask is applied. Dead-space can have a significant effect in aerosol delivery effectiveness.[28] More recently, face models have been developed that incorporate soft tissue simulation for the face itself, so that the aerosol transfer from the inhaler to the measurement apparatus can be made as realistic as possible to clinical situations.[29-31] Such models often

incorporate an anatomically realistic oro- and/or naso-pharynx so that the total mass of API arriving at a filter located at the exit is likely representative of the mass of medication deliverable to the lungs. No matter how realistically the model is constructed, unless the facemask is affixed to the face of the model with a clinically realistic force,[32] appropriate deformation of the soft tissues of the face in response to the applied pressure and associated change in dead-space between inhaler exit and the face is unlikely to be realized.[31] The use of a wrap-around belt to clamp the facemask onto the face[33] is therefore questionable, as it appears to be unrepresentative of the way a caregiver would apply a facemask. A more realistic approach would be to apply force to the facemask along the axis of the OIP/facemask to the patient. This approach was therefore taken in the development of the carriage supporting the Aerosol Delivery to the Anatomic Model (ADAM) faces.[31] Furthermore, air should not be pushed into the device by a compressor to check for facemask/face model seal integrity.[33] Instead, the air flow should be withdrawn from the OIP/facemask combination by more realistically applying a vacuum to the model exit, as would be the case if used by a patient when inhaling their medication.

Inappropriate use of the term "treatment time" in the context of nebulizer testing

Nebulizing systems are generally used to deliver medication for several minutes with typical therapy.[34] In addition to TEM itself, it is therefore useful with these delivery devices to know also the rate of aerosol delivery, TEM/measured delivery time, assuming a constant delivery rate throughout nebulization as a first approximation. However, just as there is confusion of the use of dose and TEM for the pMDI, SMI and DPI classes of OIP, so the concept of treatment time, which is really a clinical variable dependent upon the therapist, has become incorporated into the lexicon associated with laboratory testing of nebulizers. This development creates the potential for misunderstanding, both in terms of time that the nebulizer delivers medication and in estimations of medication delivery rate because laboratory test conditions may be far removed from clinical reality. For example, sampling from the nebulizer at a constant flow rate to a filter or cascade impactor downstream of the mouthpiece or facemask[35] does not reflect any effects that the continuously varying inspiratory flow rate-time profile may have on medication delivery efficiency. This deficiency is especially important with jet nebulizers that rely on air entrainment to improve medication delivery rate during inhalation, or with breath-actuated nebulizers that conserve medication when the patient exhales.[34] Furthermore, great care is needed in defining the end of medication delivery if the nebulizer is run to exhaustion of the liquid in the reservoir, because the sputtering phase that takes place just before medication delivery ceases is quite variable from one use to the next. Incorporating even part of the time associated with sputtering into so-called "treatment time"[35] can therefore be potentially misleading. A better practice is to terminate the measurement at the onset of first sputter and report the elapsed time from onset of nebulization to this juncture as "laboratory-measured delivery time." This approach is still open to interpretation, however, as it is sometimes difficult to be sure when first sputter occurs. The pharmacopeias avoid the issue by suggesting that the nebulizer is operated for a defined initial time period, the duration of which should ensure that sufficient drug substance is deposited on the inhalation filter for quantitative analysis.[3, 4] They further state that a time of 60 ± 1 seconds typically enables direct determination of the API delivery rate, but the time chosen must allow sufficient drug substance deposition on the inhalation filter to allow quantitative API analysis.

Gravimetric or chemical species assay for nebulizer-delivered TEM

The use of physiologically normal saline (0.9% w/v NaCl aqueous) or sodium fluoride solution (2.5 % w/v NaF aqueous) is often utilized as a surrogate for a solution formulation containing one or more APIs in the laboratory evaluation of nebulizer-delivered TEM.[36] However, if a gravimetric (weighing) approach, rather than an API-specific assay for such solutions, is used to report nebulizer-derived TEM, there is likely to be significant error associated with evaporation.[37] Consequently, the presentation of performance data without clarifying how the determination of TEM was undertaken[38] could therefore be misleading. The pharmacopeial methods for nebulizer performance evaluation recommend that the API substance itself be determined by chemical assay when reporting TEM and related metrics.[3, 4] It follows that the assay method should always be reported as part of the test procedure.

Beware the use of convoluted performance metrics for nebulizing systems

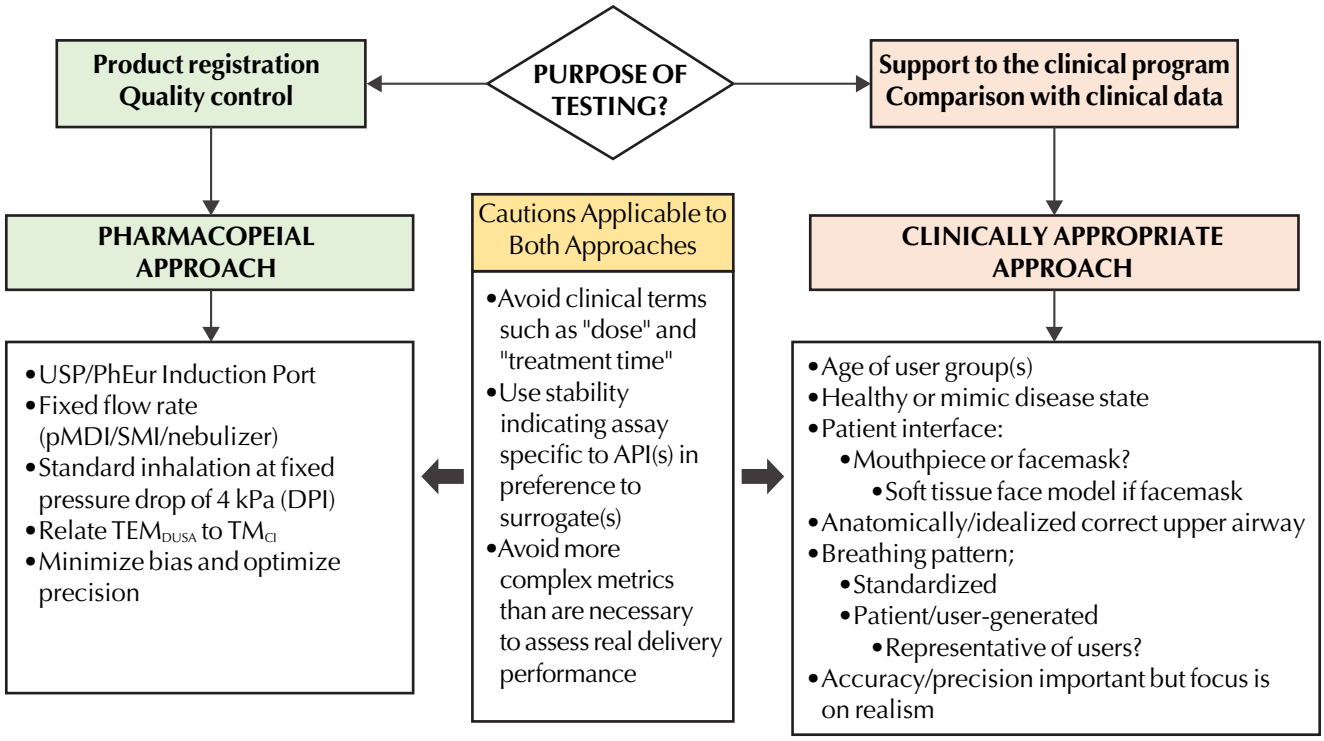
The reporting of laboratory-based performance measures based on TEM is not straightforward for nebulizing systems, chiefly because of the extended medication delivery times for these devices compared with other OIPs. In particular, for jet nebulizers, complexity in interpretation of performance data is increased because there are many ways in which the carrier gas (usually air or oxygen) can be used to convey the aerosol cloud containing the medication from the device to the patient.[34] The following are examples of pneumatic (jet) nebulizing systems:

Continuous Delivery: Continuous delivery with the aerosol contained in expanded compressed air used to create the atomization process that fragments the liquid medication into discrete droplets;

Continuous Delivery with Reservoir: Continuous delivery as above for inhalation, but with the aerosol retained in a reservoir bag or "T"-piece with extension tube during exhalation;

Figure 3

Route map approach to the laboratory evaluation of OIPs for total emitted mass



Air Entrainment: Continuous delivery with additional entrainment of room ambient air when the patient inhales;

Breath-Actuated: Air-entrainment of the aerosol during inhalation, but with no atomization during exhalation.

It follows that a variety of measures as surrogates for TEM can be created by considering how these different aerosol delivery modalities affect medication delivery.[39] Although it may be helpful to create such surrogates, especially where they might assist in indicating clinical performance, these metrics should always reflect the physical processes that take place in association with droplet generation and subsequent transport to the patient. For example, the concept of "fraction of inhalable aerosol (FIA)" has been presented by one jet nebulizer manufacturer as a common-sense approach to assessing nebulizer efficiency and performance, without the use of sophisticated aerosol lab studies.[40] This metric penalizes air entrainment nebulizers for diluting the aerosol that the patient inhales, as if nothing changes with respect to the efficiency of the aerosol generation process. FIA has therefore been used to support continuous-delivery nebulizers, which make use of aerosol conservation during exhalation, as apparently more efficient devices. However, it is well known that by increasing the flow of entrained air routed through the zone where liquid atomization takes place, the aerosol generation process is enhanced within a wide range of flow rates (hence, the alternative name "breath enhanced" for this sub-class of nebulizer).[34] Air entrainment thereby improves the delivery rate, as has clearly been shown by experimental measurements for two different nebulizers of this type, and supported with mathematical modeling of the underlying physical process.[41] On the other hand, aerosol conservation provides opportunities for droplet coagulation and deposition to interior surfaces of the conserver during the exhalation time per tidal breathing cycle, both of which waste medication. Furthermore, breath-actuated nebulizers avoid the latter altogether by only delivering medication when the patient inhales.[42] Preservation of medication can be an important consideration in the case of expensive formulations. FIA, however, fails to account for avoidance of such losses altogether. The reporting of TEM and its associated TEM/$t_{treatment}$ therefore provide a more level playing field between these different jet nebulizer types, as well as in comparisons with the newer vibrating mesh/membrane nebulizer systems.

Further considerations

The purpose of this article (and its predecessor about inhaler APSD measurements) has been to guide those involved with the laboratory evaluation of OIPs, particularly newcomers, to go through a structured thought process before developing a testing program to evaluate TEM. In particular, it is important to ensure that the correct term(s) for measurement is/are selected and understood before executing a study. Figure 3 is intended to provide a route map that can be followed, so that the purpose for testing is initially established, followed by a series of considerations that relate to development of the most appropriate test methodology for the intended approach. An analogous route should

ideally be followed if the focus is also on the determination of inhaler/aerosol generated APSD, except that the measurement apparatus will likely be a cascade impactor or laser diffractometer, rather than a DUSA or filter sampler. Although not explicitly covered here, whatever approach is taken to structure the testing program, it is assumed that Good Laboratory Practices are in place, and that consideration, at least, is given to adoption of a design-of-experiments approach that is structured to evaluate interactions between key variables as part of the quality-by-design approach that is currently preferred by regulatory agencies.[6-8]

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