

# 10 Ways to Protect Your pMDI Product

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*Methods that help reduce risk and drive  
preference in a competitive market.*

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# Introduction

With the increasing cost of drug development, advancing regulatory guidelines to protect public health and the threat of generic substitution as patents protecting molecules and delivery systems expire, pharmaceutical companies are under increasing pressure to protect and maximize revenue from existing product portfolios. In such a closely competitive environment, the integration of sound drug delivery management practices is critical to the ongoing success of a molecule.

Three key areas must be addressed:

- *Reducing the risk of product failure during development*
- *Driving preference in patients and prescribers*
- *Protecting the molecule from substitution by competitor or generic alternatives*

By following the ten best practices in this paper, you can help reduce risk, drive preference, and protect your molecule from substitution, thereby maximizing your product's chances for long-term commercial success.

## ***10 Best Practices Table of Contents***

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## Enable dose tracking for patients

*Running out of medication is a major concern for patients. Inclusion of a dose counter in pMDIs addresses that concern and helps drive preference.*



Pressurized metered-dose inhalers (pMDIs) have been around for more than fifty years and are generally regarded as the preferred method of drug delivery to the lungs for the treatment of conditions such as asthma, emphysema and chronic bronchitis. Advantages of this delivery method include reliability, accurate dosing, convenience and low cost. However, it is difficult for patients to keep track of the number of doses remaining in their inhaler, and patients have often resorted to primitive methods such as immersing the aerosol canister in water or keeping a written record to help them determine when to replace their inhalers. A survey conducted in the U.S. in 2003<sup>1</sup> found that only 36% of 342 adult asthmatics reported having been told to keep track of their pMDI doses. Additionally, 25% had found their inhaler to be completely empty when they needed it resulting in 8% needing emergency services.

Given this clear patient need for dose tracking mechanisms, the FDA published guidance in 2003 expecting new pMDI products to include an accurate means of informing patients as to the remaining number of doses left in their device. This mechanism must be an integral part of the inhaler (not an add-on) and be designed to count downwards to zero, enabling patients to know when the inhaler is reaching the end of its life. Other key criteria in the guidance can be seen in Figure 1-1.

The FDA guidance has generated a great deal of interest around dose-counting mechanisms and, while these features are neither compulsory for other regulatory bodies nor a requirement for existing products, many pharmaceutical companies are considering including a counting mechanism across their product range to help them differentiate their products from other inhalers. Additionally, by utilizing the same methods of operation, display options (individual dose by dose tracking or dose indication) and product design across a product range, a consistent “family feel” can be achieved, further differentiating products in the market.

The 3M™ Integrated Dose by Dose Counter has been designed to meet the requirements of regulators, pharmaceutical companies and patients alike. It incorporates a number of significant features including an ergonomic and robust design that has been integrated into the actuator to maintain a familiar inhaler look and feel for patients, as well as ensure compatibility with existing manufacturing lines. It utilizes a split-count design principle to match dose counter actuation as closely as possible to valve travel for solid accuracy while the individual dose-by-dose count and clear display addresses the patient's need to know when their inhaler is low. This gives patients the information they need to obtain a refill in a proactive manner, delivering clear benefits not only in peace of mind but also in condition management by allowing patients and care givers, including parents, to monitor use. This additional monitoring benefit was highlighted as a positive element during research in which the 3M Integrated Dose by Dose Counter was tested by key patient groups, including children and the elderly, to ensure the dose counter design not only met patient expectations but would enhance their experience of using a pMDI and increase their confidence in managing their disease.

**Figure 1-1 Key Criteria for Dose Counter Design**

FDA GUIDANCE	TECHNICAL REQUIREMENT	3M DOSE COUNTER
"a clear indication of when an MDI is approaching the end of its recommended number of actuations"	Individual dose by dose counter or dose indicator	Individual dose by dose counter
"integral part of the MDI canister and/or actuator, and not simply an add-on that can be removed and used multiple times"	Integral to the canister or actuator	Integral to the actuator
"Dose counters should be engineered to reliably track actuations"	Specifically, must avoid undercounting	Displacement driven split-count principle drives accuracy
"in-use studies... should address issues related to ergonomics, ruggedness, and accuracy"	Demonstrated ruggedness, accuracy and ergonomics in clinical use	Designed to be robust in the hands of patients as well as during shipping and transportation
"A lock-out mechanism to prevent doses beyond the labeled number of actuations would be an optional feature of dose counters"	Prevents patient using inhaler past zero. Not recommended for bronchodilator rescue medications	Does not include this optional feature

*Figure 1-1*  
 \*N. Sander, S Fusco-Walker, J. McElvain and B. Chipps (2006). Dose-counting and the use of pressurized metered-dose inhalers: running on empty. *Annals of Allergy, Asthma and Immunology*, 97, 1, pp34-38

SECTION **2**

## Ensure the patient receives a full dose of medication every time

*Patients who use their inhalers on an as-needed basis may improve compliance through pMDIs that utilize retention valves that do not require frequent re-priming.*

Most pMDI valves operate by refilling the metering areas as the valve stem is released after a shot is fired from the unit. If there is an extended period of time between uses, all or part of the formulation may escape the metering area. This is known as loss of prime (LOP) when referring to the propellant and loss of dose (LOD) for the active pharmaceutical ingredient (API). To protect from this, patients are generally advised to fire a priming shot if the inhaler has been left for longer than recommended. This can result in poor patient compliance either through lack of understanding or a desire to save what may be seen as a wasted dose.

While valve designs are under development that capture the dose as the inhaler is fired, eliminating the need for priming, companies can reduce the need to prime in their current products by incorporating existing retention-style valves, such as the 3M™ Retention Valve. This valve retains prime for seven or more days, helping ensure patients get accurate doses of medication even after an extended period of time between inhaler uses, giving physicians more confidence when prescribing the product.

**Figure 2-1 3M™ Retention Valve Seven Day Loss of Prime Study**

*Percentage of Initial Shot Weight*

SHOT WEIGHT	Stored Up	Stored Down	Stored Horizontal
227 Formoterol	100.5	100.3	101.2
134a Salbutamol	99.2	99.7	99.7
134a Beclomethasone	100.7	100.5	100.6

\* LOP (mean of 5 units) showing percentage of Initial Shot Weight retained after 7 days.

## SECTION 3

# Maintain a consistent appearance between sample and standard packs

*Sampling programs should take into consideration not only the medication, but also the device itself.*

Familiarity is a strong driver in instilling confidence, and consequently compliance, in asthma and Chronic Obstructive Pulmonary Disease (COPD) patients. That's why the marketing tactic that most directly effects patient change – sampling – is an important one for pharmaceutical companies. Obviously reducing the number of doses in a sample pack is desirable to both decrease the amount of expensive drug given away free, as well as drive patients to switch to a standard prescribed pack sooner.



THE 3M™ SLEEVED CANISTER

Unlike pill sample packs, though, pMDI samples offer a unique challenge since it is important not to change the size, shape or feel of the inhaler for these packs as this may undermine patient confidence. The use of a low fill canister, such as the 3M™ Sleeved Canister, which houses a smaller medicine chamber within a standard sized canister, enables sampling of both the medication and the pMDI device to help drive preference and maintain confidence while improving profit margins with smaller samples.

## SECTION 4

# Improve formulation stability and product performance

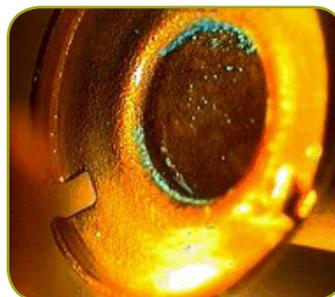
*Formulation stability improves product performance and increases shelf life to help decrease waste and improve profitability.*

In pMDIs the API is formulated with a hydrofluoroalkane (HFA) propellant (plus excipients if required) within the container closure system (CCS). Depending on its molecular properties, the API may be formulated as suspension or, through the addition of a co-solvent, a solution. Both routes can lead to interaction between the API and the CCS. For suspension formulations the interaction can cause deposition on the canister wall and exposed surfaces of valve components, which can lead to a reduction in drug content of the formulation. For solution formulations, interactions more commonly cause degradation leading to both reduced drug content and increased impurity levels.

Coatings, like those offered by 3M, can be applied to the canister and valve components to protect the contents from deposition and degradation. This will improve performance and help extend a product's shelf life.



UNTREATED METERING TANK



FLUORINATED ETHYLENE PROPYLENE COATED METERING TANK

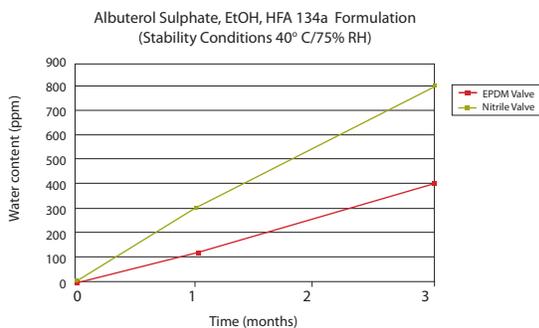
# Utilize proven technology in new developments

*The use of proven technology can help mitigate risk while building on patient familiarity to help deliver patient and prescriber preference.*

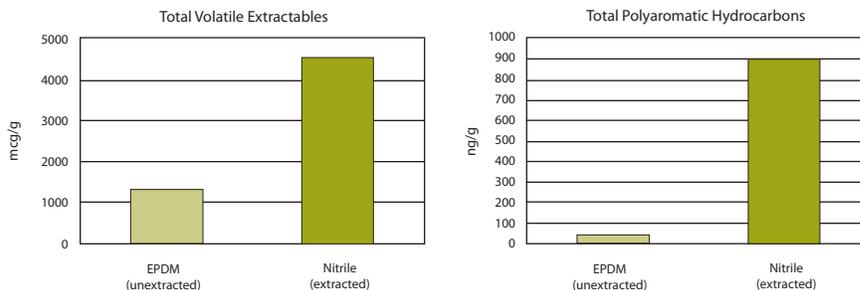
Introducing new technology during product development can add additional time and risk to projects, including potential rejection by patients who may be unwilling to gamble on unfamiliar delivery methods. Utilizing proven, patient-friendly technology that has been updated for today's molecules delivers the reassurance that necessary pharmaceutical performance criteria, such as dose delivery, can be accomplished without jeopardizing the product's timeline or chances for technical success.

One example is the 3M™ Retention Valve. This all-metal valve based on the proven Spraymiser™ model (the original retention valve) helps to ensure the valve performs under a wide variety of conditions and patient use regimes. With the addition of a clean Ethylene-Propylene Diene Terpolymer (EPDM) elastomer the valve offers low extractable and leachable levels, low moisture ingress and low levels of elastomer swell while maintaining fundamental performance features such as the ability to be pressure filled and uniformity of delivered dose. The following charts illustrate key performance factors for the 3M™ Retention Valve.

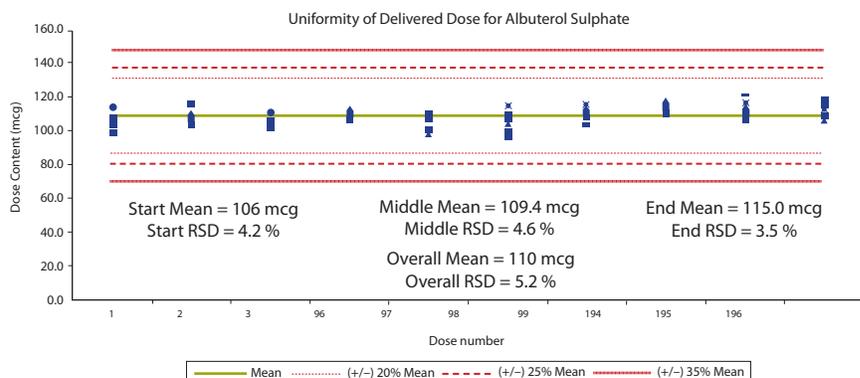
**Figure 5-1**  
Relative Moisture Ingress for 3M valves utilising EPDM and nitrile elastomers



**Figure 5-2**  
Extractables levels for extracted Nitrile elastomer compared with unextracted EPDM elastomer



**Figure 5-3**  
Uniformity of Delivered Dose for Albuterol Sulphate, ethanol, HFA134a formulation, 3 months 40° C/75%RH



*Adding features that improve patient experience can help pharmaceutical companies defend their products against generic substitution.*



THE 3M™ AUTOHALER™

## Differentiate products in the marketplace

The continuing escalation in product development costs means pharmaceutical companies are under increasing pressure to find ways to increase revenues from existing products and to stem sales erosion following the launch of generic equivalents. By enhancing products through improvements to delivery technologies and the addition of features to improve performance in the hands of patients, pharmaceutical companies can prolong patent protection, defend their brands against generic substitution and open up opportunities to engage new patients.

There are a number of technologies in development which may enhance patient experience. The addition of a dose counter to alert patients as to when to replace their inhaler and enable them to more accurately monitor use is one such example (see section 1). Another opportunity is to offer breath-actuated operation. The basic principle of the pMDI requires patients to press and breathe simultaneously. While many patients are able to coordinate these actions adequately to receive an effective dose, some patients find it difficult and may benefit from the use of a breath-activated device, such as the 3M™ Autohaler™. The Autohaler device was developed by 3M to trigger actuation as the patient breathes in, helping ensure patients receive their full dose of medication. During 2008 3M will have produced more than 100 million Autohaler devices, which have been incorporated into products such as Airomir™, Qvar™ and Maxair™.

Other technologies may be incorporated which, while not as obvious to the patient, offer significant improvement in terms of product performance. For example, because most patients do not understand how pMDIs work, they are unaware of the importance of shaking their inhalers correctly or of priming their inhalers after periods of non-use. New valves, such as the 3M™ Face Seal Valve currently under development by 3M, have been designed to address this issue. The 3M Face Seal Valve is a new type of pMDI valve that captures the dose as the inhaler is operated, negating the need for the patient to prime the inhaler before use. Its design not only meets the regulatory expectations for product performance, but is also more robust in real-life patient usage.

Lifecycle management may also offer a route to increased revenue from existing pMDI products. This is especially true of APIs with potential applications in other therapies, such as allergic rhinitis, since expansion of existing pulmonary products into another format, in this case nasal, uses much of the original technology. Focusing changes on the actuator, and utilizing the existing formulation and container closure system data plus experience gained from the original development program, can significantly speed up the development process. Additionally, some aspects, such as certain toxicology and extractables studies (assuming no changes are made to contact materials), may not need to be repeated for the new submission, further speeding the route to product approval. Overall, creating new applications for existing molecules and extending their lifecycles can deliver a substantial return on investment when compared with the full development program required for new drug substances.

## SECTION 7

*To be successful, your pharmaceutical product must be readily available and consistently manufactured over the course of its lifecycle.*

### Ensure long-term manufacturability

Having the right product at the right time is only half the story. Companies must be able to maintain a product's positive momentum throughout its lifecycle to help ensure success. That means that when choosing a manufacturing partner, companies must consider not only the cost of individual components but also the consistency and robustness of the manufacturing processes if manufacturability is to be maintained over the product lifetime and batch release costs are to be kept to a minimum.

Additionally, a manufacturing partner must have the flexibility to quickly scale-up production as needed from development through commercialization to keep the product development pipeline ahead of the competition while still meeting the requirements of regulators and customers with cGMP compliant practices.

As a leading drug delivery developer, 3M has extensive expertise in the field of manufacturing. From pilot to full-scale production, use of state-of-the-art processes enables cost-effective, on-time delivery with the highest level of customization and quality. However, it is the 3M team's experience and expertise that separates 3M from the competition. With a long track record of innovative problem solving and successful New Drug Applications (NDAs), 3M offers customers complete support and documentation for the development of new molecules as well as delivery optimization and enhancement for already established products.

# Bring the patient voice to product development

*Putting patients at the heart of development benefits pharmaceutical companies through improved compliance and increased patient and prescriber preference.*

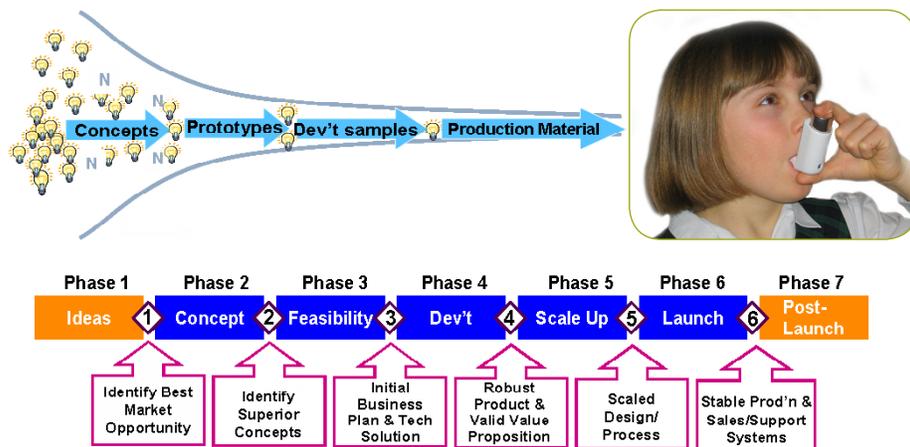
Bringing new products to market is a slow process. As developments progress it is important to consider patient needs as well as determine probability of acceptance of new drug delivery options. Putting patients at the heart of drug delivery product design can accelerate the process of bringing products to market in a patient-friendly way and drive patient and prescriber preference. Improvements that enhance the patient experience can increase patient preference for an individual product and increase prescribers' confidence that the patients can, and will, use the device correctly. Patient-friendly enhancements not only differentiate the product from competitors but also drive loyalty, helping to protect the product from substitution.

From the beginning, when the first pMDI was inspired by a young patient who was struggling with a glass bulb nebulizer, 3M has developed products and technologies with a patient focus. Today 3M continues to invest in global research in order to understand how patients interact with inhalers.

It is ideal to have several stages of patient research. Exploratory research looking at broad customer needs and gaps in technologies should be conducted on a regular basis to initiate development opportunities. Once early concepts have been developed they can be tested with patients, allowing revisions to be made according to the responses obtained. Ideally the final product solution should be validated with patients before large financial commitments are made to scale-up and commercialize products. Finally, no system would be complete without ensuring that learning gained throughout development and launch is fed back into new product ideas and concepts.

With this in mind, a New Product Introduction system (Figure 8-1) was specially designed for 3M to include in-depth customer focus throughout the development process alongside the more traditional technical, manufacturing and business deliverables.

*Figure 8-1*  
New Product Introduction System (Product development and commercialization)



This level of experience is critical when conducting patient research to ensure research design is robust. To deliver true value, studies must be carefully thought out if findings are to be representative of actual uptake following launch. The consequences of not doing so can be commercially disastrous. It has been suggested that this may have contributed to the lack of uptake of Exubera™. Patients willing to enter clinical studies for non-injection delivery of insulin may have been a patient group more predisposed to learning new techniques for delivery than the general patient population. It is critical to consider such eventualities when planning research.

Each program of patient research conducted enhances the overall understanding of patient lifestyles, inhaler interaction and general preferences and, as such, it is important to ensure learning from one project can be fed back along the development process into others.

Through this methodology 3M was able to use previous research to understand the primary patient needs for the inclusion of a dose tracker in the design of their Integrated Dose by Dose Counter. During concept design, 3M's designers were able to utilize previous research to focus on the following criteria indicated by patients as the most important:

- *Displays individual count*
- *Retains inhaler look and feel*
- *Accurate*
- *Fits in hand*
- *Robust design stands up to real-life use*

These features were validated during patient research, which compared this configuration to other approaches. By putting patients at the center of development, customers can be assured that 3M products and technologies will be well-received by patients and prescribers alike.

## Utilize new technology to enable the delivery of “difficult” formulations

*New anti-flocculating components can negate the need to reformulate or abandon a formulation when dosing irregularities caused by rapid flocculation occur.*

Most current pMDI formulations are comprised of suspensions of one or more micronized active compounds in a hydrofluoroalkane (HFA) based propellant system. Such formulations have a tendency of rapid flocculation followed by either creaming or sedimentation, depending on the relative density of the solids to the propellant mixture. This can lead to inconsistent dosing if the formulation is not re-dispersed sufficiently before the next dose is taken.

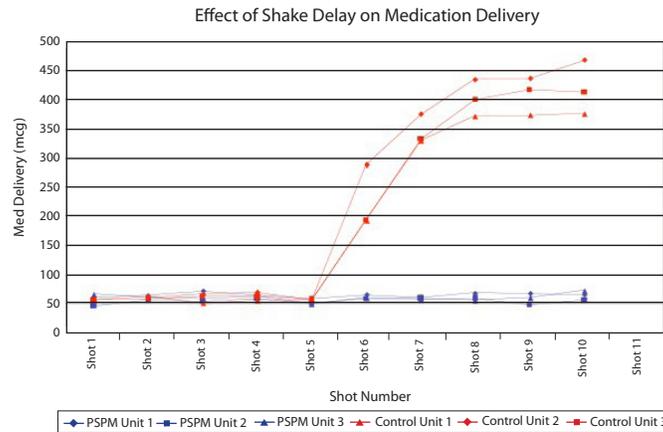
To overcome this problem 3M Drug Delivery Systems has developed a unique semi-permeable system component to act in synergy with a flocculating suspension formulation. This particulate semi-permeable matrix (PSPM) technology has been shown to improve the dosing uniformity of these rapidly flocculating formulations and therefore can negate the need to reformulate or even abandon a formulation when dosing irregularities caused by rapid flocculation are encountered. Medication delivery results for a zero ethanol HFA 134 albuterol formulation tested can be seen in figure 9-1.

In this study units containing the PSPM technology were tested against control units. Units were primed and then shots 1 to 10 were collected and analysed for medication delivery. Shots 1 to 4 were fired using a standard shake technique and shots 5 to 10 were fired following a 30 second delay after shaking. Results clearly show the PSPM technology delivers a consistent dose even after the rapidly flocculating formulation has sedimented following shake delay. The new technology was recognized as one of the most innovative ideas presented at the Drug Delivery to the Lungs conference in Edinburgh in 2006 and was awarded the annual poster prize.



*DETAIL OF RETICULATED FOAM*

**Figure 9-1**  
Effect of 3M PSPM Technology on Medication Delivery (ex Actuator) following Shake Delay



## SECTION 10

# Reduce product development risk

*By reducing risk, companies can optimize product development pipelines to bring better products to market, faster.*

Out of all the drug candidates selected for development in the pharmaceutical industry, only a few make it to clinical trials. Fewer still go on to become successful, profitable products. To shift the odds in your favor, companies should seek out and utilize experienced partners, proven processes and increasingly advanced technologies to help reduce risk.

**Figure 10-1**  
Kelly, John M.D. The Drug Discovery, Development and Approval Process. [www.phrma.org](http://www.phrma.org).

		Clinical Trials				
Discovery/Preclinical Testing		Phase I	Phase II	Phase III	Phase IV	
Years	6.5	1.5	2	3.5	1.5	15 total
Test Population	Lab and animal studies	20 to 100 healthy volunteers	100 to 500 patient volunteers	1,000 to 5,000 patient volunteers	Review process/ approval	Additional post-marketing testing required by FDA
Purpose	Assess safety, biological activity and formulations	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use		
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved	

3M Drug Delivery Systems offer more than 50 years of experience and proven success in inhalation technologies. From unique formulations and mechanical challenges to global regulatory support, 3M can draw on its vast community of experts as well as leading-edge technologies to reduce risk, solve issues and deliver a customized solution. It's part of an ongoing culture of innovation that's created a lot of firsts, including the first pressurized Metered-Dose Inhaler (pMDI), the first non-CFC pMDI, and the first single cycle review for a pMDI in the USA.

From pilot to full scale, 3M can provide a competitive advantage in reliability and flexibility with a full range of cGMP compliant development and manufacturing capabilities that can be customized to your specific needs. With state-of-the-art facilities currently producing more than 60 million pMDIs for worldwide distribution each year, 3M has the capacity to meet your needs now and in the future. Lean Six Sigma methodology ensures quality and consistency throughout the life of your product.

# When you need drug delivery results, experience matters.

3M Drug Delivery Systems offers more than 50 years of experience and proven success in technology, product development and manufacturing, coupled with our global regulatory expertise. We can offer a partnership that ensures a smooth process from start to finish and help you bring your products to market more quickly. Working with us, you get the speed to market that's critical to the success of your new application.

ENABLING YOUR SUCCESS.

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