ADVANCES IN PULMONARY DELIVERY OF INHALED ANTI-INFECTIVES

With the growing problems caused by antimicrobial resistance, there is increasing interest in the use of improved strategies for drug delivery. David L. Hava, PhD, Chief Scientific Officer, Pulmatrix, explores the benefits of nebulised inhaled antibiotics delivered via high throughput nebulisers for aqueous formulations or dry powder inhalations for cystic fibrosis patients.

Pulmonary infectious diseases afflict millions of people annually, with significant morbidity and mortality associated with bacterial, viral and fungal infections. Patients with respiratory disease are particularly susceptible to infection, where respiratory infections are associated with exacerbations of disease and worsening lung function. The impact of infectious diseases and the growing threat of antimicrobial resistance have heightened the need for novel anti-infectives and led to incentives aimed at the pharmaceutical industry to discover and develop drugs to meet this need.

INHALED DRUG DELIVERY OF ANTI-INFECTIVES

A complementary approach to improving anti-infective therapies is to develop improved strategies for drug delivery that enable higher therapeutic indices and higher drug concentrations at the sites of infection. This strategy has been especially effective in the development of inhaled antibiotics for cystic fibrosis (CF) patients with *Pseudomonas aeruginosa* infection (Table 1). Due to impaired mucociliary clearance and mucus accumulation in the airways, patients with CF become colonised with a number of different bacteria early in life and eventually become chronically colonised with pathogens such as *P aeruginosa*.

> "In the specific case of inhaled anti-infectives, given the high drug loads required for efficacy in the lung, lactose-based technologies are inadequate to deliver these drug in sufficient quantities. Therefore, novel DPI technologies are required to enable anti-infective products for inhalation."

In a landmark study, Ramsey *et al* studied the effect of inhaled tobramycin on pulmonary function and *P aeruginosa* infection in CF patients over a 24-week period.[1] They found that patients treated with inhaled tobramycin had an increase in FEV1 of 10% and decreased *P aeruginosa* density in sputum at week 20 compared with placebo. Importantly, inhaled tobramycin was not associated with accumulation of drug in plasma or the ototoxicity and nephrotoxicity that can be associated with systemically delivered aminoglycosides.[2,3]

This study led to the approval of

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Drug product	Drug substance	Target	Format	Company	Status
TOBI®	tobramycin	*P aeruginosa*	Nebulized	Novartis	Approved
TOBI® Podhaler™	tobramycin	*P aeruginosa*	DPI	Novartis	Approved
Cayston®	aztreonam	*P aeruginosa*	Nebulized	Gilead	Approved
Colobreathe®	colistin	*P aeruginosa*	DPI	Forest	Approved (EU)
Arikace™	amikacin	NTM	Nebulized	Insmed	Phase 3
Ciprofloxacin DPI	ciprofloxacin	*P aeruginosa*	DPI	Bayer	Phase 3
AeroVanc™	vancomycin	MRSA	DPI	Savara	Phase 3
Pulmaquin™	ciprofloxacin	*P aeruginosa*	Nebulized	Aradigm	Phase 3
FTI	fosfomycin - tobramycin	*P aeruginosa*	Nebulized	CURx	Phase 3
FAI	fosfomycin - Amikacin	Gram negative bacteria / VAP	Nebulized	Cardeas	Phase 2
PUR1900	itraconazole	*Aspergillus spp*	DPI	Pulmatrix	Preclinical

Table 1: Current inhaled anti-infective therapies approved or in development

Tobramycin Inhalation Solution (TOBI®; Novartis AG, Basel, Switzerland) in 1999, for the management of CF patients with *P aeruginosa*. TOBI is supplied as a liquid solution to be used with a reusable jet nebulizer (Pari LC Plus, PARI, Midlothian, VA, US) and an air compressor. TOBI is administered twice daily, with each administration taking approximately 15 minutes to complete.[4]

Subsequently, a second antibiotic, aztreonam, has been developed as a nebulised liquid formulation by Gilead (Cayston®; Gilead, Foster City, CA) for similar use, with other nebulised products in development (Table 1).

The development of nebulised inhaled antibiotics provided a major advance to address significant unmet need in CF. While nebulised products are suitable for patients in a hospital setting, such as those with ventilator-associated pneumonia (VAP), the formulation of inhaled antibiotics into a portable, user-friendly format is desired to reduce treatment burden and improve compliance.

High throughput nebulisers for aqueous formulations or dry powder inhalers (DPI) have been two approaches to solve this challenge. For decades, lactose blends have been the cornerstone of inhaled dry powder therapies for asthma and chronic obstructive pulmonary disease (COPD), where small doses of drug, typically less than 500 µg are required for efficacy. Lactose-based DPI, formulations are created with small, respirable (<5 µm) crystalline drug particles blended with large particles of micronised lactose (~150 µm), whereby the drug particles detach from the lactose carrier during inhalation and the drug is then available for delivery to the lung (Figure 1a, next page).

> "The majority of inhaled anti-infective approaches have focused on the treatment of P aeruginosa infection, with more recent programs focused on MRSA and non-tuberculoid mycobacterium."

This technology has been successfully applied to potent small molecules and small molecule combinations for COPD and asthma. In the specific case of inhaled anti-infectives, given the high drug loads required for efficacy in the lung, lactose-based technologies are inadequate to deliver these drug in sufficient quantities. Therefore, novel DPI technologies are required to enable anti-infective products for inhalation.

Particle engineering using spray drying allows for the manufacture of dry, respirable particles that can be loaded with high weight percentages of drug. Early technologies that utilised this approach, Pulmospheres™ (Novartis AG, Basel, Switzerland) and the ARCUS™ technology (Acorda Therapeutics, Ardsley, NY, US), were developed as low-density, porous particle technologies in which geometrically large particles (>5 µm) could be manufactured such that the particle morphology resulted in particles with small aerodynamic size.[5,6]

The resulting particles overcome several major limitations of lactose blend DPIs: obviated the need for lactose blending by avoiding the use of highly cohesive small drug particles,[7] improved delivery efficiency to the lungs and allowed for delivery of high drug loads. Pulmospheres are the underlying technology used to develop TOBI Podhaler™, a dry powder version of tobramycin.

In clinical trials, TOBI Podhaler™ efficacy was comparable with the inhalation solution,[8,9] yet results in lower total drug exposure (112 mg dry powder to 300 mg nebulised) in a drug product configuration that allows the dose to be administered in only a few minutes using a portable system. A number of other dry powder formulations are advancing through clinical development (Table 1), including ciprofloxacin DPI (Bayer HealthCare Pharmaceuticals, Whippany, NJ, US) for treating *P aeruginosa* and AeroVanc™ (Savara Inc, Austin, TX, US) for methicillin-resistant *Staphylococcus aureus* (MRSA).

A more recently developed particle engineering technology, iSPERSE™ (Pulmatrix Inc, Lexington, MA, US) leverages advantages of both the first generation spray drying technologies and small, dense drug particles to enable unique inhalation products for treating respiratory disease. In contrast to Pulmospheres and ARCUS particles, iSPERSE particles are both geometrically and aerodynamically small with higher density particles (typical tapped densities >0.4 g/cc).

In contrast to small and dense neat drug particles that require lactose blending for drug dispersibility (Figure 1a), iSPERSE particles (Figure 1b) are dispersible in the absence of carrier and result in consistent drug delivery to the lungs independent of inspiratory flow rate and patient effort. Due to the high density of the particles, iSPERSE-based products can be developed across a range of DPI technologies, including capsule, blister and reservoir-based devices.

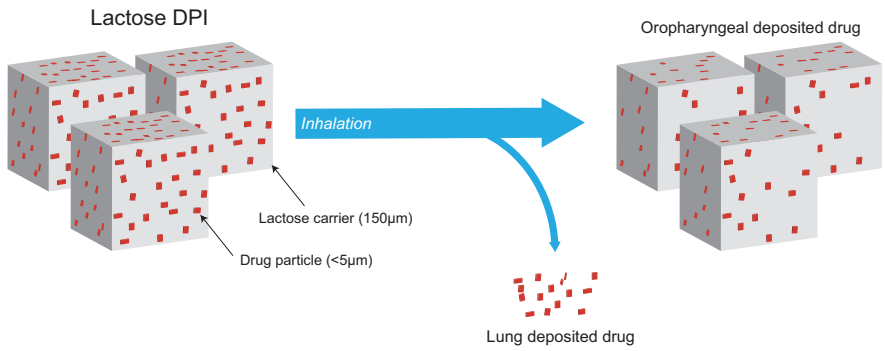

Figure 1a: Lactose DPI are formulated with crystalline, micronized drug particles (red) blended with large lactose particles. During inhalation, drug particles detach from the lactose carrier allowing a fraction of the drug to be inhaled into the lungs. Due to their large size, the lactose particles, with remaining attached drug, deposit in the oropharyngeal cavity and are swallowed.[7]

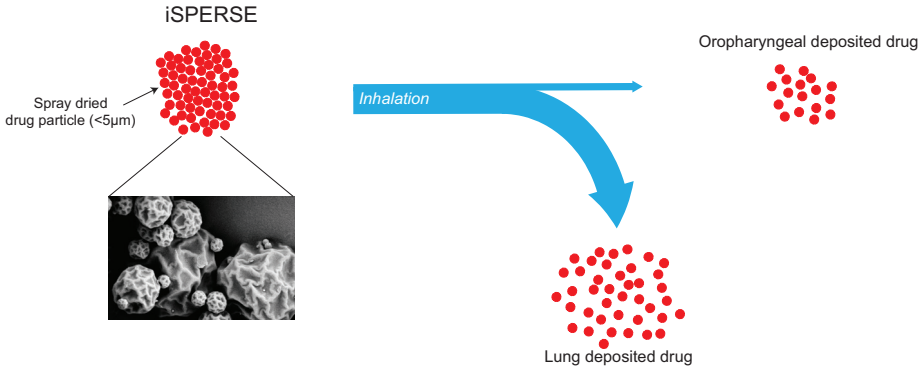

Figure 1b: Spray dried iSPERSE particles are formulated with drug & excipients in the same particle with no need for blending. Upon inhalation, the small drug particles readily disperse and a high fraction (>50%) of the particles are delivered to the lung, with a smaller fraction depositing in the oropharynx. The resulting efficiency results in 3-4 times the amount of drug delivered to the lungs compared with lactose DPI.

MORBIDITY AND MORTALITY OF PULMONARY FUNGAL INFECTIONS

The majority of inhaled anti-infective approaches have focused on the treatment of *P aeruginosa* infection, with more recent programs focused on MRSA and non-tuberculoid mycobacterium (NTM). In addition to bacterial infections, pulmonary fungal infections, particularly those caused by the spore-forming mould *Aspergillus fumigatus* cause significant morbidity and mortality in a number of patient populations.

A fumigatus is the predominant species causing disease, however, other species such as *A niger*, *A terrus*, *A flavus* infect humans as well. Pulmonary *A fumigatus* infections manifest as a range of diseases depending on the host immune state and underlying lung disease.[10] In immunocompromised hosts, invasive pulmonary aspergillosis (IPA) is a life-threatening disease occurring in patients with impaired immunity as a result of treatment for haematological cancers, solid organ transplantation or other immunosuppressive conditions.

The mortality rate of IPA in neutropenic and hematopoietic stem-cell transplant recipients is >50% and 90%, respectively.[11,12] Because of the significant mortality associated with IPA, antifungal prophylaxis is used to reduce the risk of infection.

A fumigatus also causes chronic infection in patients with chronic lung disease such as asthma, COPD and CF. *Aspergillus spp* are the most common fungi present in the lungs of patients with CF, with *A fumigatus* being predominant.[13,14] CF patients with chronic *A fumigatus* infection have lower percent predicted FEV1 than uninfected controls and persistently infected patients have a higher rate of hospitalisations for pulmonary exacerbations.[15]

Pulmonary infection with *A fumigatus* can cause allergic bronchopulmonary aspergillosis (ABPA), an allergic response resulting from hypersensitivity to fungal antigens. ABPA is characterised by a local and systemic eosinophilic and IgE inflammatory response, and acute exacerbations that lead to worsening lung function.[10] Chronic *Aspergillus* infection and ABPA are not commonly associated with invasive aspergillosis.

The annual burden of chronic aspergillosis and ABPA is significantly higher than that of IPA, with more than 3 million cases of chronic disease and 4.8 million cases of ABPA annually (www.gaffi.org).[16] The majority of ABPA represents disease in asthmatics, which equates to 1-2.5% of all asthmatics worldwide. In CF, reports of ABPA prevalence vary from 1 to 15%,[17] with reports of colonisation rates in respiratory samples ranging from 6 to 58%.[15,16,18]

New methods to detect *Aspergillus spp* in sputum using quantitative PCR and galactomannan ELISA have the potential to increase significantly the sensitivity of detection and ultimately, diagnosis. These techniques have been used recently to classify patients into four subgroups; those without aspergillosis, those sensitised to *Aspergillus spp*, those with ABPA and those with aspergillus bronchitis.[16]

Using this methodology, Baxter *et al* classified 130 CF patients and found that 30% had aspergillus bronchitis and 17.7% had ABPA. Armstead *et al* extended these findings by comparing these rates with the reported rates of ABPA in CF registries and literature reports for adult CF patients from 30 different countries.[19] They found that the number of ABPA cases diagnosed and reported is likely a significant under-

representation of the estimated cases when more sensitive diagnostic assays are utilised. Of particular interest, in the US the number of documented adult CF cases of ABPA (869 cases) was 34.6% of the estimated cases (2510 cases) defined by Armstead *et al*. Using the more recent data, almost 50% of US adult CF patients are predicted to have either ABPA or aspergillus bronchitis.[19]

Anti-fungal treatment regimens for ABPA and aspergillus bronchitis commonly rely on oral triazoles, such as itraconazole and voriconazole, that inhibit fungal cytochrome P450 synthesis of ergosterol, a critical component of the fungal cell wall.[20] ABPA is a more severe disease than aspergillus bronchitis where oral corticosteroid therapy is recommended, with the addition of oral itraconazole to treatment regimens in certain situations.[17] Long-term oral steroid use, while effective at reducing inflammation, is associated with severe side effects that must be managed and monitored.[21] Oral corticosteroid side effects have led to intense efforts to develop steroid sparing agents for a number of diseases including ABPA.

Oral itraconazole therapy has a demonstrated benefit in the treatment of aspergillus bronchitis[22] and ABPA,[23-25] and a number of case reports and case studies have demonstrated a benefit of antifungal therapy in treating ABPA in both CF and non-CF patients.[26] Two randomised, placebo-controlled studies have explored the anti-inflammatory effect and clinical response to oral itraconazole in asthmatics with ABPA.[23,24]

These studies both describe a benefit of oral itraconazole therapy *versus* placebo. Stevens *et al*[24] performed a 16-week double blind, placebo-controlled randomised study in 55 asthmatics with ABPA, with a 16-week open label extension in which all patients received oral itraconazole. The primary endpoint was the clinical response to therapy, defined as a combination of decreasing corticosteroid use and decrease in systemic IgE, with either an improvement in lung function or exercise tolerance.

The study found a significant improvement in clinical response in the itraconazole group compared with placebo (13/28 *versus* 5/27; p=0.04), with more than 70% of patients reducing oral corticosteroid dose by 50% or more. Notably, 12 of 33 patients who did not respond in the double blind portion of the study had a clinical response in the open label extension.[24] In a complementary study, Wark *et al* studied the impact of oral itraconazole on pulmonary inflammation by assessing sputum eosinophilia and sputum levels of eosinophil cationic protein (ECP) in 29 stable patients with ABPA.[23] Itraconazole therapy was associated with a significant drop in sputum eosinophils over the first month of therapy (35% reduction *versus* placebo; p<0.01) that was maintained over 16 weeks. Similar effects were seen with ECP in sputum and in serum levels of IgE and *Aspergillus*-specific IgG.

The results from the studies by Wark *et al* and Stevens *et al* are supportive of broader and more consistent use of antifungal therapy to treat ABPA. Two smaller studies have examined the role of oral itraconazole in treating ABPA in CF patients. Denning *et al* evaluated itraconazole therapy in six ABPA patients, three of which had CF.[25] All three CF patients successfully reduced corticosteroid use, and two of the three showed substantial clinical improvement, including improved lung function and reduced serum IgE.

> "Clinical development of PUR1900 is planned to initiate in 2016 and comes at a time when there is an urgent need for novel anti-fungal drugs and a relatively sparse development pipeline."[36]

A larger case series studied 16 CF patients with ABPA.[27] Itraconazole use was associated with reductions in corticosteroid use (47% reduction) and acute exacerbations (55% reduction). Due to the increased risk of long-term steroid use on the development of diabetes, osteoporosis and growth, the opportunity to reduce steroid use through the treatment with oral itraconazole is highly desired.[28,29]

LIMITS OF CURRENT ANTI-FUNGAL TREATMENTS

Despite the promise of oral itraconazole and triazoles in the treatment of aspergillus bronchitis and ABPA, these therapies have significant limitations that limit their long-term utility (Table 2). Limitations include side effects such as hepatoxicity and phototoxicity with voriconazole, variability in the bioavailability of itraconazole following oral dosing and extensive drug-drug interactions (DDI) due to the metabolism of azoles in the liver.

Variability in the achieved plasma levels of itraconazole have been reported in a number of studies and suggested as a variable that may account for inconsistent clinical responses.[25,27] Oral bioavailability of itraconazole in healthy volunteers is 55%, which may be further reduced in patients with poor digestive function.[30]

Itraconazole pharmacokinetics (PK) following oral dosing have been evaluated in CF patients. An exploratory PK study in 12 CF patients ≥16 years old and five CF patients <16 years old examined plasma concentrations of itraconazole and its active metabolite, hydroxy (OH)-itraconazole, over 14 days.[31] After eight days, steady-state concentrations were achieved with high inter-subject variability. None of the young patients and only 50% of the older patients achieved steady-state itraconazole trough concentrations >250 ng/mL. Plasma concentrations of >250 ng/mL have been defined as the target trough concentration required to get sufficient itraconazole lung levels to treat infection.[32]

These results were similar to a second study that examined serum and sputum concentrations in 11 CF patients with ABPA aged 5-15 years.[33] Five patients failed to reach itraconazole plasma trough concentrations >250 ng/mL at steady state. Additionally, sputum concentrations of itraconazole were variable across patients, with five of 11 failing to achieve sputum concentrations above the reported 90% minimum inhibitory concentration (MIC90) for *A fumigatus* both at trough and 4h after oral dosing. Inconsistency in itraconazole exposure systemically and consequently in the lung may account for some of the variability in clinical responses.

A larger trial aimed at studying the therapeutic benefit of oral itraconazole in CF patients failed to show a clinical benefit of itraconazole, with the majority of patients failing to achieve therapeutic blood levels of itraconazole.[34] Thus, despite the potential benefit of treating ABPA and aspergillus bronchitis with itraconazole, it is challenging to achieve consistently high exposure in plasma and lungs, with oral dosing. An inhaled version of itraconazole via DPI could seemingly overcome these limitations and provide a better option for patients.

Attribute	Oral delivery	Inhaled delivery
Total dose	> 400 mg daily	< 40 mg daily
Lung to plasma exposure ratio	Low	High
Bioavailability	55% - itraconazole > 95% - voriconazole	> 60% directly to site of infection
Lung exposure	Variable; affected by diet	Consistently high
Side effects	Systemically and orally driven • Gastrointestinal • Phototoxicity (Voriconazole) • Drug-drug interactions	Locally driven

Table 2: Oral versus inhaled itraconazole.

BENEFITS OF INHALED ANTI-FUNGALS OVER CONVENTIONAL THERAPIES

PUR1900 or Itraconazole Inhalation Powder, is a dry powder formulation of itraconazole formulated in the iSPERSE platform technology. PUR1900 is engineered to have a small aerosol particle size for efficient pulmonary delivery and is intended to be delivered using a capsule-based DPI. PUR1900 formulations in development have mass median aerosol diameters (MMAD) of ~3 µm and high fine particle doses (FPD; % of the nominal dose < 5 µm), resulting in more than 50% of the nominal dose reaching the lungs. Notably, the aerosol target range of PUR1900 is similar to that of *Aspergillus* conidia, allowing for itraconazole delivery to lung sites where fungal spores also deposit upon inhalation.

Pulmonary delivery of itraconazole is expected to overcome many limitations of oral anti-fungal therapies (Table 2). PUR1900 enables the delivery of high doses of itraconazole (>10 mg) to the lungs that exceed both the minimum inhibitory concentration of itraconazole against *A fumigatus* and the levels achieved with oral dosing, while limiting systemic exposure. The profile of achieving high lung concentrations and low plasma concentrations reverses the profile achieved with oral dosing where high plasma concentrations are needed for achieving therapeutic lung levels. In Figure 2, plasma concentration is depicted for an orally dosed drug (aqua) and an inhalation drug (purple). Oral dosing (A) results in high plasma concentrations that may lead to toxicity or drug-drug interactions. High plasma exposure is necessary to achieve therapeutic exposure in the lungs. In contrast, inhaled dosing requires less exposure overall and results in significantly less systemic exposure. Inhaled dosing (B) achieves higher local concentrations in the lung that significantly exceed the minimum inhibitory concentration (MIC) of the drug over a long period of time. Due to the direct delivery of high concentrations of drug directly to the lung, the achieved pulmonary concentrations following inhalation may greatly exceed those achieved by oral dosing.

High lung concentrations achieved through inhalation may increase the time that lung drug levels remain above the minimum inhibitory concentration of itraconazole, a critical parameter of triazole efficacy,[35] and may further lead to concentrations that achieve fungicidal activity. Low plasma exposure following inhalation will reduce the risk of drug-drug interactions, which is especially important since azoles affect the PK of recently approved CFTR modulators that will be widely used by CF patients. The lower systemic exposure is also expected to ease the side-effect burden in the CF patients.

Clinical development of PUR1900 is planned to initiate in 2016 and comes at a time when there is an urgent need for novel anti-fungal drugs and a relatively sparse development pipeline.[36] The mainstays of current anti-fungal therapy centre on azoles, echinocandins and amphotericin B, each with limitations in both activity, convenience of dosing (IV *versus* oral) and toxicity. While drugs with novel mechanisms of action are in development, these come with the added risk of both uncertain activity and unknown toxicities in man. Similarly, new drugs in existing drug classes must be studied comparatively with standard of care to demonstrate safety or efficacy benefits to support their adoption.

As a reformulation of a drug with years of clinical data, known activity and addressable limitations via inhalation, PUR1900 has the potential to provide a valuable addition to current treatment options for pulmonary fungal diseases.

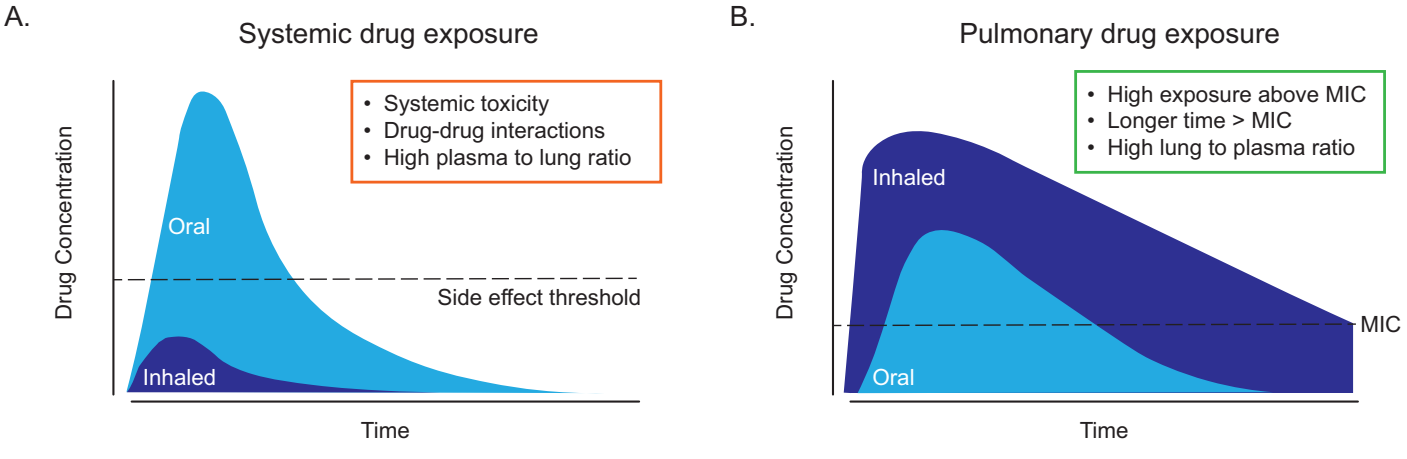

Figure 2: Inhaled delivery of anti-fungal increases lung exposure while reducing systemic exposure that leads to side effects.

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