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Weill Cornell Medical College
1300 York Avenue, Box 70
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March 7, 2022

Re: Docket No. FDA-2013-P-1001

Dear Drs. Carson and Reidenberg:

This letter responds to your citizen petition dated September 12, 2013 (Petition), requesting that the Food and Drug Administration (FDA or Agency) "add a warning to the labeling of all nonprescription drug products containing an ingredient with anticholinergic or histamine H1 inverse agonist effects" (Petition at 1).[1] In your Petition, you state that the impairment of thinking caused by these ingredients can cause a confusional state. You also state that taking drug products with these ingredients in conjunction with other drugs with similar effects can result in an acute confusional state or delirium, especially in the elderly. You request the addition of a warning that would state that products containing ingredients with anticholinergic or histamine H1 inverse agonist effects can cause confusion, impaired attention, disorientation, and decreased power of concentration (Petition at 1).

We have carefully considered your Petition, the comments submitted to the docket, and other information available to the Agency. For the reasons described in detail below, your Petition is denied.

I. BACKGROUND

Your Petition requests that a warning be added to the labeling of over-the-counter (OTC) drugs with anticholinergic or histamine H1 inverse agonist effects. Your discussion is limited, however, to OTC drugs with anticholinergic effects. Some drugs with histamine H1 inverse agonist effects have anticholinergic effects, but some do not. Conversely, some drugs with anticholinergic effects do not have histamine H1 inverse agonist effects. Like your Petition, this response addresses OTC drugs with anticholinergic effects, whether or not they have histamine H1 inverse agonist effects.

[1] The Petition dated September 12, 2013, is a corrected version of the Petition. An earlier version dated August 12, 2013, was also submitted to FDA and is included in the docket.

A. Antihistamines With Anticholinergic Effects

1. OTC Monographs and New Drug Applications

Drugs with histamine H1 inverse agonist effects, commonly known as antihistamines, can be divided into two categories, first-generation antihistamines, many of which are marketed pursuant to the OTC Drug Review, and second-generation antihistamines, which are marketed under either new drug applications (NDAs) and abbreviated new drug applications (ANDAs). First-generation antihistamines can have anticholinergic effects.

Antihistamines' mechanism of action is related to the H1 receptor. An antihistamine acts as an inverse agonist on the H1 receptor by stabilizing the receptor in its inactive state. This blocks the action of histamine peripherally, alleviating the symptoms of allergies. First-generation antihistamines, however, are non-selective and also bind to other receptors, including anticholinergic receptors. This can result in cognitive impairment, drowsiness, dry eyes, dry mouth, constipation, and urinary hesitancy or retention. Second-generation antihistamines are more selective for the H1 receptor than first-generation antihistamines are, reducing the potential for anticholinergic effects.

The effects of antihistamines on mental status are not due solely to their anticholinergic properties. H1 receptors are found in the brain and other organs and are thought to play a role in cognition. First-generation antihistamines act on these H1 receptors as well as those that cause the symptoms of allergies, leading to central nervous system (CNS) side effects such as sedation and impaired mental alertness.

Many of the first-generation antihistamines have been determined to be generally recognized as safe and effective under the Cold, Cough, Allergy, Bronchodilator, and Antihistamine Drug Products for Over-the-Counter Human Use final monograph (21 CFR Part 341) (CCABA FM). Antihistamines covered by the CCABA FM may be indicated "'[f]or the temporary relief of runny nose, sneezing, itching of the nose or throat, and itchy watery eyes due to hay fever' (which may be followed by one or both of the following: 'or other upper respiratory allergies' or '(allergic rhinitis).'" The first-generation antihistamine clemastine fumarate is indicated for the relief of similar symptoms. It is not covered by the CCABA FM and antihistamine drug products containing clemastine fumarate are marketed under approved drug applications.

In addition, two first-generation antihistamines, diphenhydramine hydrochloride and diphenhydramine citrate, are generally recognized as safe and effective for the relief of occasional sleeplessness by individuals who have difficulty falling asleep under the Nighttime Sleep-Aid Drug Products for Over-the-Counter Human Use final monograph (21 CFR part 338) (Nighttime Sleep-Aid FM). A third first-generation antihistamine, doxylamine succinate, is likewise indicated for use to help reduce difficulty falling asleep. Drug products containing doxylamine succinate for this indication are marketed under approved drug applications.

The first-generation antihistamines cyclizine hydrochloride, dimenhydrinate, diphenhydramine hydrochloride, and meclizine hydrochloride are generally recognized as safe and effective for the prevention and treatment of nausea, vomiting, or dizziness associated with motion sickness under the Antiemetic Drug Products for Over-the-Counter Human Use final monograph (21 CFR part 336) (Antiemetic FM).

When combined with other OTC ingredients, first-generation antihistamines have additional uses. For example, fixed-dose combination drugs containing diphenhydramine citrate or diphenhydramine hydrochloride and either a nonsteroidal anti-inflammatory drug or acetaminophen are used to relieve occasional sleeplessness associated with minor aches and pains and to help fall asleep and stay asleep.

2. Current Warnings in Labeling

Under the CCABA FM, products containing the first-generation antihistamines brompheniramine maleate, chlorcyclizine hydrochloride, chlorpheniramine maleate, dexbrompheniramine maleate, dexchlorpheniramine maleate, phenindamine tartrate, pheniramine maleate, pyrilamine maleate, thonzylamine hydrochloride, or triprolidine hydrochloride include the following warning:

> "May cause drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery." (21 CFR 341.72(c)(3)).

The Antiemetic FM requires the same warning for products containing cyclizine hydrochloride or meclizine hydrochloride. (21 CFR 336.50(c)(6)). The labeling for clemastine fumarate similarly warns that drowsiness may occur, that alcohol, sedatives, and tranquilizers may increase drowsiness, that alcoholic drinks should be avoided, and that users of the product should be careful when driving a motor vehicle or operating machinery.

The CCABA FM requires that the labeling for products containing diphenhydramine citrate, diphenhydramine hydrochloride, or doxylamine succinate include a stronger warning, as follows:

> "May cause marked drowsiness; alcohol, sedatives, and tranquilizers may increase the drowsiness effect. Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor. Use caution when driving a motor vehicle or operating machinery." (21 CFR 341.72(c)(4)).

The Antiemetic FM requires the same warning for products containing dimenhydrinate or diphenhydramine hydrochloride (21 CFR 336.50(c)(7)), while the Nighttime Sleep-Aid FM requires this, more limited, one for products containing diphenhydramine citrate or diphenhydramine hydrochloride:

> "Avoid alcoholic beverages while taking this product. Do not take this product if you are taking sedatives or tranquilizers, without first consulting your doctor." (21 CFR 338.50(c)(4)).

The warning regarding the products' potential to cause marked drowsiness is not required for products marketed under the Nighttime Sleep-Aid FM because that monograph covers products that are indicated for use to help reduce difficulty falling asleep. The labeling for doxylamine succinate similarly warns against the use of alcoholic beverages when using the product and states that it should only be taken at bedtime. The labeling for fixed-dose combination drugs containing diphenhydramine citrate or diphenhydramine hydrochloride and either a nonsteroidal anti-inflammatory drug or acetaminophen warns that drowsiness will occur and warns against consuming alcoholic drinks, driving a motor vehicle, or operating machinery.

Approved OTC histamine H2 inverse agonists, commonly known as H2 blockers, including cimetidine 100-milligram (mg) and 200-mg oral tablets, ranitidine hydrochloride 75-mg and 150-mg oral tablets, and famotidine 10-mg and 20-mg oral tablets, have relatively weak, if any, anticholinergic effects and so do not bear a similar warning.

B. Other Over-the-Counter Drugs With Anticholinergic Effects

OTC drugs other than the first-generation antihistamines may also have anticholinergic effects. One OTC drug product with anticholinergic effects is Oxytrol for Women (oxybutynin 3.9 mg transdermal system), which was marketed under an NDA and is used for overactive bladder in women. On March 3, 2016, FDA approved revised labeling for Oxytrol for Women that includes the following warning: "Sleepiness, dizziness, confusion, and blurry vision may occur. Do not drive or operate machinery until you know how the patch affects you."

C. Legal and Regulatory Framework

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that all drug labeling bear adequate directions for use and adequate warnings against unsafe use (21 USC 352(f)). The regulations set forth warnings that must be included, if applicable, in the labeling of every OTC drug (21 CFR 201.63; 21 CFR 201.66(c)(5)). The OTC drug monographs contain additional warnings specific to a therapeutic class or to particular drugs within a therapeutic class.

In order to change nonprescription drug labeling to strengthen existing warnings, data establishing the link between such OTC drugs and clinically significant side effects are necessary. You have not provided adequate scientific evidence necessary to support your request for the addition of the warnings to the labeling of OTC products with anticholinergic effects.

As discussed further below, based on our review of the information that you provided and our scientific expertise, we do not consider your request to add warnings to the labeling of these OTC drug products to be warranted at this time or supported by the evidence submitted in your Petition. Consequently, we deny the request in your Petition.

II. DISCUSSION

In your Petition, you request the addition of a warning to the labeling of OTC products with anticholinergic effects, stating that such products can cause confusion, impaired attention, disorientation, and decreased power of concentration. We discuss below the previous Agency activity related to anticholinergic and CNS side effects of first-generation antihistamines, our review of the literature submitted in your Petition as well as other available information, and our review of your request for labeling changes.

A. Previous Agency Activity

The anticholinergic and CNS side effects of first-generation antihistamines have long been recognized as a concern both within and outside FDA.

For example, FDA has worked with the National Transportation Safety Board (NTSB) since 2000 to increase public awareness about drugs that may increase the risk of motor vehicle accidents, including first-generation antihistamines. Since 2006, FDA has released several communications, geared towards consumers, addressing the safety of taking certain medications and driving, including, "Driving When You Are Taking Medications"[2] and "Some Medications & Driving Don't Mix."[3] In addition, the National Highway Traffic Safety Administration (NHTSA) released a public service announcement warning the public about drugs that may increase the risk of motor vehicle accidents.[4] In 2019, the Agency released the consumer update "Seasonal Allergies: Which Medication is Right for You?" that discussed the CNS affects of the OTC first-generation antihistamines.[5]

In 2013, FDA explored whether the recommended dose for the OTC first-generation antihistamines should be reduced or modified to reduce the risk of next-morning impairment, particularly when driving or operating heavy machinery. FDA reviewed data and information characterizing the pharmacokinetics and pharmacodynamics of OTC first-generation antihistamines covered by the CCABA monograph. FDA found no published pharmacokinetic or pharmacodynamic data supporting a dose-response relationship for individual first-generation antihistamines.

In 2013 and 2014, FDA evaluated whether the labeling of first-generation antihistamines adequately described the CNS effects of these drugs and conveyed the risk of next-morning impairment. As part of this evaluation, the Agency reviewed its Adverse Event Reporting System (FAERS) database, the National Electronic Injury Surveillance System – Cooperative

[2] "Driving When You Are Taking Medications." FDA, 07 Feb. 2022, https://www.fda.gov/drugs/resources-you-drugs/driving-when-you-are-taking-medications.
[3] "Some Medications and Driving Don't Mix," FDA, 07 Feb. 2022 https://www.fda.gov/consumers/consumer-updates/some-medicines-and-driving-dont-mix.
[4] "Heavy Machinery - Female 30." NHTSA, 07 Feb. 2022, https://www.youtube.com/watch?app=desktop&v=QJGCH80sOes.
[5] "Seasonal Allergies: Which Medication is Right for You?" FDA, 07 Feb. 2022, https://www.fda.gov/consumers/consumer-updates/seasonal-allergies-which-medication-right-you.

Adverse Drug Event Surveillance (NEISS-CADES) database, and published literature for serious adverse events that may suggest CNS impairment, such as accidents, emergency department visits, and falls associated with the use of first-generation antihistamines covered by the CCABA monograph. The FAERS review revealed relatively few such events considering the large volume of use of these products. The NEISS-CADES data showed that, on average, there were fewer than 2,000 antihistamine-related emergency department visits associated with CNS impairment annually between 2004 and 2011. The reported symptoms were in general not life-threatening (e.g., dizziness, somnolence) and most patients were treated and released from the emergency department. Based on its review of the postmarketing data and published literature, FDA concluded at that time that the monograph labeling adequately describes the CNS effects associated with first-generation antihistamines and that additional regulatory action was not warranted because the reported frequency of serious adverse events was relatively modest given the widespread use and decades of marketing of these drugs.

B. Literature Regarding Anticholinergic Effects

In your Petition, you ask FDA to add a warning to the labeling of all OTC drugs with anticholinergic effects, stating that such products can cause confusion, impaired attention, disorientation, and decreased power of concentration. You state that as early as 1971 it was suggested in case reports that medications with anticholinergic effects could cause a confusional state, and you describe some of the information that has been developed in the intervening years, focusing on the impact of these medications on the elderly. In addition to case reports, the information you rely on derives from medical textbooks, scientific articles, and a clinical practice guideline.

FDA has read and analyzed each of the 14 references you cite in your Petition. Four of the references are medical textbooks that do not present original data.[6] Six of the references present data from studies of prescription anticholinergic drugs or from studies of anticholinergic drugs generally.[7] Data from non-OTC anticholinergic drugs are not directly applicable to the assessment of OTC anticholinergic drugs because of important considerations specific to the particular drug, treatment indication, dose, and duration of use. Published studies support that there is heterogeneity in the effects of different anticholinergic drugs. Later in this section, we discuss studies which report an increased risk of cognitive effects in more general categories of anticholinergic drugs, but not in subgroup analyses that include OTC anticholinergic drugs.

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[6] Brunton, LL, Chabner BA, Knollmann BC, eds., Goodman and Gilman's The Pharmacologic Basis of Therapeutics, New York, McGraw Hill, 2011, pp. 918-919; Goldman L, Schafer AI, eds. Goldman's Cecil Medicine, 24th ed., New York, Elsevier, 2012, p. 670; Halter JB, et al. Hazzard's Geriatric Medicine and Gerontology, 6th ed. New York, McGraw Hill, 2009, p. 765; Roper AH, Samuels MA, eds. Adams and Victor's Principles of Neurology, New York, McGraw Hill, 2009, pp. 404, 406.

[7] Cai X, et al., 2012, Long-term Anticholinergic Use and the Aging Brain. Alzheimer's and Dementia, 9: 377-385; Janowsky DS, et al., 1972, Letter to the Editor. Amer J Psychiatry, 129: 360-361; Perry EK, et al., 2003, Increased Alzheimer Pathology in Parkinson's Disease Related to Antimuscarinic Drugs. Ann Neurol, 54:235-238; Pomara N, et al., 2008, Increased Mental Slowing Associated with the APOE e4 Allele after Trihexyphenidyl Oral Anticholinergic Challenge in Healthy Elderly. Am J Geriatr Psychiatry, 16: 116-124; Sunderland T, et al., 1987, Anticholinergic Sensitivity in Patients with Dementia of the Alzheimer Type and Age-Matched Controls. Arch Gen Psychiatry, 44:418-426; Tune L, et al., 1992, Anticholinergic Effects of Drugs Commonly Prescribed for the Elderly: Potential Means for Assessing Delirium. Am J Psychiatry, 149: 1393-1394.

Two of the references are population-based observational studies that you assert are two of many "showing worse performance in elderly taking drugs with anticholinergic activity" (Petition at 2). In the first population-based observational study that you cite, of the 27 anticholinergic drugs listed as being used by study participants, only one is an OTC antihistamine.[8] In the second of these studies, only 1 of 364 subjects used an OTC antihistamine.[9]

One of the references is a systematic review of published rankings of drugs based on the drugs' anticholinergic activity in the elderly.[10] Three OTC antihistamines, chlorphenamine, dexchlorpheniramine, and diphenhydramine, were included on the review's list of 100 anticholinergic active ingredients. Using pooled scores from the published rankings, the review classified each of the 100 ingredients as either a high- or a low-potency anticholinergic. All three of the OTC antihistamines on the list were classified as high-potency, but the review did not explore their effect on cognitive impairment.

The final reference that you cite is the American Geriatric Society's 2012 Beers Criteria for Potentially Inappropriate Medication Use in Older Adults.[11] The 2012 Beers Criteria include a "strong" recommendation against prescribing first-generation antihistamines to older adults in most circumstances. The publication cites evidence that these drugs are highly anticholinergic, that clearance is reduced with advanced age, that tolerance develops when used as a hypnotic, and that use carries an increased risk of, among other things, confusion. No assessment specific to OTC first-generation antihistamines is available as part of the 2012 Beers Criteria. The publication states that "the intentions of the criteria are to improve the selection of prescription drugs by clinicians and patients . . . ."[12] It is unclear to what extent OTC first-generation antihistamines were considered in the 2012 Beers Criteria assessments. Four of the 12 first-generation antihistamines that were assessed are not available OTC, including the 2 cited as having the highest quality of evidence for anticholinergic effects (i.e., hydroxyzine, promethazine).

In addition to reviewing the literature cited in your Petition, we conducted our own review of the scientific literature regarding anticholinergic drugs. As noted previously, we have also been monitoring the anticholinergic and CNS side effects of first-generation antihistamines for many

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[8] Ancelin ML, et al., 2006, Non-Degenerative Mild Cognitive Impairment in Elderly People and Use of Anticholinergic Drugs: Longitudinal Cohort Study. BMJ, 332:445

[9] Landi F, et al., 2007, Anticholinergic Drugs and Physical Function among Frail Elderly Population. Clin Pharmacol Ther, 81:235-241.

[10] Durán CE, et al., 2013, Systematic Review of Anticholinergic Risk Scales in Older Adults. Eur J. Clin Pharmacol, 69:1485-1496.

[11] American Geriatrics Society 2012 Beers Criteria Update Expert Panel, 2012, American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 60:616-631. The Beers Criteria were updated in 2015 and 2019, but the recommendation regarding first-generation antihistamines remained the same. American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015, American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 63:2227-2246. American Geriatrics Society 2019 Beers Criteria Update Expert Panel, 2019, American Geriatrics Society 2019 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019 Apr;67(4):674-694.

[12] Id.

years. A 2012 systematic review identified 162 randomized, double-blind, placebo-controlled trials evaluating amnestic and non-amnestic mild cognitive impairment caused by medications with anticholinergic, antihistamine, GABAergic, or opioid effects.[13] Some studies of first-generation antihistamines reported decreased alertness with disturbances in attention and vigilance. Cognitive impairment was reported in studies of 2 prescription first-generation histamine H1 antagonists, hydroxyzine and promethazine. Word recall impairment was reported with diphenhydramine 100 mg dosing but not with lower doses of diphenhydramine ranging from 25-75 mg. OTC doses of diphenhydramine are 25-50 mg.

Additional studies support that there is heterogeneity in the effects of different anticholinergic drugs. These studies report an increased risk of cognitive effects with anticholinergic drugs overall, but not in analyses of subgroups that include antihistamines. A nested case-control study by Coupland, et al reported that exposure to several types of anticholinergic drugs is associated with an increased risk of dementia.[14] However, adjusted analyses did not provide evidence of an increased risk of dementia with use of antihistamines (95% confidence intervals included the null value of 1).

A case-control study by Richardson, et al reported associations between some classes of anticholinergic drugs and future dementia incidence.[15] Drugs were categorized using the World Health Organization Anatomical Therapeutic Chemical Classification System, in which OTC antihistamines are categorized as respiratory. The study did not provide evidence of an increase in the association between dementia incidence and respiratory anticholinergic drugs (95% confidence intervals included the null value of 1).

A prospective population-based cohort study by Gray, et al[16] reported that, overall, higher cumulative anticholinergic use is associated with an increased risk for dementia. However, analyses by anticholinergic drug subtype (eTable 2) provided evidence for an increase in risk for dementia with antidepressants but not for other anticholinergic drug classes.

In your Petition, you state that "[t]he degree of impairment relates to the . . . total amount of anticholinergic activity received by the person." In our assessment, the relationship between an individual's anticholinergic drug burden and the degree of resulting impairment is unknown. A review published in 2014 that evaluated observational studies of anticholinergic burden in relation to CNS adverse effects in older adults was inconclusive.[17] Of the 19 studies (published between 1988 and 2013) that the authors reviewed, 9 showed no statistically significant relationship between the total amount of anticholinergic activity and cognitive impairment, while the remaining 10 studies did find a statistically significant relationship. These conflicting

[13] Tannenbaum C, et al., 2012, A Systematic Review of Amnestic and Non-Amnestic Mild Cognitive Impairment Induced by Anticholinergic, Antihistamine, GABAergic and Opioid Drugs. Drugs & Aging, 29:639-658.
[14] Coupland CAC, et al., 2019. Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. JAMA Intern Med. 179(8):1084-1093.
[15] Richardson K, et al. 2018. Anticholinergic drugs and risk of dementia: case-control study. BMJ. 25;361:k1315.
[16] Gray SL, et al. 2015. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. JAMA Intern Med. 175(3):401-7.
[17] Kersten H & Bruun Wyller T, 2014, Anticholinergic Drug Burden in Older People's Brain – How Well Is It Measured?, Basic & Clin Pharm & Tox, 114:151-159.

findings may be due to the lack of consensus on how to best measure the anticholinergic activity of a medication. In addition, there appears to be a wide degree of heterogeneity in individuals' sensitivity to anticholinergic medication.

C. Your Request for a Labeling Change

Currently, OTC drugs with anticholinergic effects bear the warnings regarding their potential to cause CNS effects such as drowsiness that are described in sections I.A. and I.B of this response. While the literature supports a general association between anticholinergic drugs and other CNS effects, including cognitive impairment, in most cases these are data predominantly derived from non-OTC anticholinergic drugs. Data from non-OTC anticholinergic drugs are not directly applicable to the assessment of OTC anticholinergic drugs, because of important considerations specific to the particular drug, treatment indication, dose, and duration of use. It is FDA's scientific judgment that the existing warnings provide adequate directions for use for OTC drugs with anticholinergic effects.

Your Petition suggests that these OTC drugs need additional warnings because patients may attribute a confused state to something other than OTC drug products, which they perceive as safe. We are not aware of formal evaluations of patients' perceptions of adverse events due to nonprescription drug products with anticholinergic activity or histamine H1 inverse agonist effects. FDA's decision to add a warning to an OTC drug does not depend on whether patients are or are not likely to attribute a side effect to the drug.

Given that little safety data specific to OTC first-generation antihistamines or other OTC drugs with anticholinergic effects are currently available, we do not believe that changing nonprescription drug labeling to strengthen existing warnings is warranted at this time. In addition to the lack of sufficiently specific safety data, the review FDA conducted in 2013 and 2014 revealed that relatively few serious adverse events related to CNS impairment have been reported in association with first-generation antihistamines. In the absence of sufficient data to support the regulatory action you seek, the Agency believes the current warnings found on the labeling of OTC drugs with anticholinergic effects, as well as the consumer outreach and education efforts, are adequate to convey the message that first-generation antihistamines and other OTC drugs with anticholinergic effects have CNS side effects. FDA will also continue to evaluate new and existing data and information on the safety of OTC first-generation antihistamines and other OTC drugs with anticholinergic effects and may take additional action in the future if additional data or information become available.

III. CONCLUSION

Based on the reasons described in this response, we deny your Petition. As with all drug products, we will continue to monitor the safety of OTC drugs with anticholinergic effects and take further action if we determine it is appropriate.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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Patrizia Cavazzoni, M.D.
Director
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