UNITED STATES
CONSUMER PRODUCT SAFETY COMMISSION
4330 EAST WEST HIGHWAY
BETHESDA, MD 20814

This document has been electronically approved and signed.

DATE: September 1, 2021

BALLOT VOTE SHEET

TO: The Commission
Alberta E. Mills, Secretary

THROUGH: Jennifer Sultan, Acting General Counsel
Mary T. Boyle, Executive Director

FROM: Daniel R. Vice, Assistant General Counsel, Regulatory Affairs
David M. DiMatteo, Attorney, Regulatory Affairs

SUBJECT: Petition to Exempt Baloxavir Marboxil (XOFLUZA™) in 40 mg and 80 mg Tablet Doses from Special Packaging Requirements of the Poison Prevention Packaging Act

BALLOT VOTE DUE: Wednesday, September 8, 2021

Attached is a briefing package from staff concerning a petition submitted by Genentech, Inc., requesting exemption for baloxavir marboxil, which it markets as XOFLUZA™ in 40 mg or 80 mg tablet doses from special packaging requirements under the Poison Prevention Packaging Act (PPPA). Staff recommends that the Commission grant the petition and publish a notice of proposed rulemaking. A draft *Federal Register* notice is provided at Tab F of the staff briefing package.

Please indicate your vote on the following options:

I. Grant Petition PP 20-1, and approve publication in the *Federal Register* of the draft notice of proposed rulemaking without change.

_____ _____
(Signature) (Date)

II. Grant Petition PP 20-1, and approve publication in the *Federal Register* of the draft notice of proposed rulemaking, with changes (please specify changes):

_____

_____

_____

_____

_____ _____

(Signature) (Date)

III. Deny Petition PP 20-1, and direct the staff to prepare a letter of denial to the petitioner.

_____ _____

(Signature) (Date)

IV. Defer decision on Petition PP 20-1.

_____ _____

(Signature) (Date)

V. Take other action (please specify):

_____

_____

_____

_____

_____ _____

(Signature) (Date)

Attachment: Draft *Federal Register* notice: Poison Prevention Packaging Requirements; Proposed Exemption of Baloxavir Marboxil Tablets in Packages Containing Not More than 80 mg of the Drug

Briefing Package

Petition to Exempt XOFLUZA™ (PP 20-1) from the Special Packaging Requirements of the Poison Prevention Packaging Act

For Information:
Cheryl Scorpio, Ph.D.
Directorate for Health Sciences
240-987-2572

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Executive Summary

Genentech petitioned the U.S. Consumer Product Safety Commission (Commission or CPSC) to exempt XOFLUZA™ 40mg and 80mg tablets from special packaging requirements. CPSC staff recommends that the Commission grant the petition pursuant to 16 CFR § 1702.17(a) because the firm has met the requirements to receive an exemption under the regulation. Specifically, staff determined that available data support that XOFLUZA has low oral toxicity, and there have been no serious adverse event data associated with accidental ingestion. The data reviewed by CPSC staff show that "special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance.". 16 CFR § 1702.17(a).

XOFLUZA is used to treat the flu and is taken in one dose within 48 hours of experiencing symptoms. XOFLUZA was originally approved by the Federal Drug Administration (FDA) in October 2018, with a two-tablet dose that was in child-resistant packaging (CRP). In March 2021, the FDA approved single-tablet doses of XOFLUZA. Genentech maintains that XOFLUZA is not acutely toxic, and therefore, it does not require CRP.

In addition, the firm wants to move its XOFLUZA manufacturing to [redacted] where, the firm states, it is unable to package XOFLUZA in CRP because the material used for the child-resistant configuration requires specialized equipment that is not readily available at the new location. Accordingly, Genentech maintains that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA because it will be unable to package XOFLUZA in special packaging at its new manufacturing facility.

The Poison Prevention Packaging Act (PPPA) requires "special packaging" or CRP for certain "household substances," with requirements codified at 16 CFR § 1700 and 16 CFR § 1702. Specifically, the PPPA requires that the Commission issue regulations mandating special packaging if:

> (1) the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance; and
> (2) the special packaging to be required by such standard is technically feasible, practicable, and appropriate for such substance.

15 USC § 1472(a). CPSC has implemented this provision of the PPPA by promulgating a regulation requiring special packaging for oral prescription drugs. 16 CFR § 1700.14(a)(10). The Commission's regulations allow a firm to petition for an exemption from the special packaging requirements for several reasons, including that a substance has a "lack of toxicity and lack of adverse human experience for the substance [that] clearly supports granting the exemption," 16 CFR § 1702.7(a), or that "special packaging is not technologically feasible, practicable, or appropriate for the substance.". 16 CFR § 1702.7(b). Either one of these reasons may be a basis

for granting an exemption. If the Commission determines that reasonable grounds for an exemption are presented by the petition, CPSC regulations require publication in the *Federal Register* of a proposed amendment to the listing of substances that require special packaging, stating that the substance at issue is exempt. 16 CFR § 1702.17.

Staff determined that available data support that XOFLUZA has low oral toxicity, and there have been no serious adverse event data associated with accidental ingestion. Thus, staff believes the firm has shown that "special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting the substance," and therefore, concludes that the firm has met the requirements to receive an exemption from the special packaging requirements under 16 CFR § 1702.17(a). The acute toxicity of XOFLUZA is mild and may include diarrhea, nausea, and headache. For these reasons, staff recommends that the Commission grant the petition to exempt XOFLUZA from special packaging requirements in packages containing not more than 80 mg of the drug.

In the regulation at 16 CFR §1700.14 (a), the CPSC has determined that the listed substances require special packaging, and likewise, concluded that the special packaging must be technically feasible, practicable, and appropriate. For packaging to be considered feasible, the technology must be available to produce packaging that conforms to established standards.[1] For packaging to be considered practicable, it must be adaptable to modern mass production and assembly line techniques.[2] Packaging is considered appropriate if the packaging will adequately protect the integrity of the substance it contains and will not interfere with its intended storage or use.[3] The petitioner's request for exemption must comply with 16 CFR §1702.7(b), which states: "If the exemption is requested because special packaging is not technologically feasible, practicable, or appropriate for the substance, the justification shall explain why."

The petitioner indicates that currently, "XOFLUZA is packaged at a [redacted] facility in [redacted], which has the equipment necessary to manufacture packaging that meets the Commission's child resistant packaging requirements."[4] Genentech provided documentation demonstrating its current packaging materials conform to FDA guidelines. Therefore, the petitioner has effectively demonstrated that it is technically feasible, practicable, and appropriate to package XOFLUZA in special packaging that meets U.S. requirements. However, the firm has not demonstrated that it is not technically feasible, practicable, or appropriate to package XOFLUZA at the site in [redacted]. Therefore, an exemption from special packaging on that basis is not warranted

[1] S. Rep. 91-845, at 10 (1970).
[2] Ibid.
[3] Memorandum from Charles Wilbur, HSPS. to Jacqueline Ferrante. Ph.D. HSPS. "Technical Feasibility. Practicability, and Appropriateness Determination for the Proposed Rule to Require Child-Resistant Packaging for OTC Products Containing Ketoprofen." August 20, 1996.
[4] Covington & Burling, LLP, March 30, 2020.

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

Briefing Memorandum September 1, 2021

To: The Commission
Alberta Mills, Secretary

Through: Jennifer Sultan, Acting General Counsel
Mary Boyle, Executive Director

From: Cheryl Scorpio, Ph.D., Project Manager
Directorate for Health Sciences

Subject: Petition to Exempt XOFLUZA™ from the Special Packaging Requirements of the PPPA

I. Introduction

The Poison Prevention Packaging Act (PPPA) requires "special packaging" or CRP for certain "household substances," with requirements codified at 16 CFR § 1700 and 16 CFR § 1702. Specifically, the PPPA requires that the Commission issue regulations mandating special packaging if:

> (1) the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting such substance; and
> (2) the special packaging to be required by such standard is technically feasible, practicable, and appropriate for such substance.

15 USC § 1472(a). CPSC has implemented this provision of the PPPA by promulgating a regulation requiring special packaging for oral prescription drugs. 16 CFR § 1700.14(a)(10). The Commission's regulations allow a firm to petition for an exemption from the special packaging requirements for several reasons, including that a substance has a "lack of toxicity and lack of adverse human experience for the substance [that] clearly supports granting the exemption," 16 CFR § 1702.7(a), or that "special packaging is not technologically feasible, practicable, or appropriate for the substance.". 16 CFR § 1702.7(b). Either one of these reasons may be a basis for granting an exemption. If the Commission determines that reasonable grounds for an exemption are presented by the petition, CPSC regulations require publication in the *Federal*

Register of a proposed amendment to the listing of substances that require special packaging, stating that the substance at issue is exempt. 16 CFR § 1702.17.

In March 2020, the Commission received a petition from Genentech, Inc., requesting to exempt the tablet forms of their marketed drug, XOFLUZA™ (Baloxavir Marboxil) from CRP requirements. XOFLUZA was approved by the Federal Drug Administration (FDA) in October 2018, with a two-tablet dose for the acute uncomplicated flu in patients greater than 12 years old showing symptoms for less than 48 hours. In March 2021, the FDA approved the single-tablet doses of XOFLUZA. Currently, XOFLUZA is in tablet form and dispensed in CRP.

The Commission voted unanimously (4-0) **not** to approve publication of a draft *Federal Register* notice seeking public comments on Petition PP 20-1, from Genentech, Inc., requesting that the Commission exempt XOFLUZA from the special packaging requirements of the PPPA. Staff advised against publication of the draft *Federal Register* notice because the petition provided all available information necessary for staff to make its technical recommendation under the PPPA.

The petitioner maintains that there are reasonable grounds for an exemption from PPPA special packaging requirements because: (1) special packaging is not required to protect children from serious illness resulting from ingesting XOFLUZA; and (2) special packaging is not technically feasible, practicable, or appropriate for XOFLUZA. For packaging to be considered feasible, the technology must be available to produce packaging that conforms to established standards.[5] For packaging to be considered practicable, it must be adaptable to modern mass production and assembly line techniques.[6] Packaging is considered appropriate if the packaging will adequately protect the integrity of the substance it contains and will not interfere with its intended storage or use.[7]

The petitioner further asserts that requiring special packaging for XOFLUZA may hamper Genentech's ability to respond quickly and efficiently to an increased demand for the drug, which serves a significant public benefit in reducing the risk of a flu epidemic. The firm contends that there is a compelling public health interest in granting this petition for exemption.

II. Discussion

A. Toxicity

The Directorate for Health Sciences staff reviewed the toxicity of XOFLUZA. Overall, treatment with XOFLUZA is well tolerated. If accidentally ingested, the greatest potential for injury is

[5] S. Rep. 91-845, at 10 (1970).
[6] Ibid.
[7] Memorandum from Charles Wilbur, HSPS. to Jacqueline Ferrante. Ph.D. HSPS. "Technical Feasibility. Practicability, and Appropriateness Determination for the Proposed Rule to Require Child-Resistant Packaging for OTC Products Containing Ketoprofen." August 20. 1996.

diarrhea, nausea, and headache. For these reasons, Health Sciences Staff determined that XOFLUZA will not cause serious injury or death upon acute exposure by a child under 5 years old.

[redacted]. XOFLUZA also has been studied in pediatric patients (Hirotsu, 2019; Heo, 2018; NCT03653364, CAPSTONE 2; Hayden, 2018; Dziewiatkowski et al., 2019). Overall, clinically relevant doses of XOFLUZA (40 or 80 mg total dose) are well tolerated in humans (Dziewiatkowski et al., 2019; Taieb et al., 2019; Ng, 2019; Hayden, 2018).

The analysis of total adverse events (AE) included 10 studies with 6 treatments and 5628 patients. AE did not differ significantly between placebo and XOFLUZA. For drug-related vomiting, 3297 patients from 5 studies were included. XOFLUZA did not differ from placebo in these studies (Taieb et al., 2019). Of 610 patients (12 to 64 years old), the percentage of patients experiencing any adverse event[9] in the CAPSTONE 1 clinical trial was 1.0% grade 3 or grade 4, which can be categorized as not serious. Five deaths have been reported by the FDA Adverse Event Reporting System Database (FAERS)[10]; however, these deaths have been determined not to be related to XOFLUZA.

The most common adverse event (AE) of the correct dose of XOFLUZA was diarrhea (Heo, 2018; Shionogi prescribing info). The XOFLUZA Product Information, 2021 reported that diarrhea (3%), bronchitis (3%), nausea (2%), and headache (1%) were the most significant AEs found.

Treatment of an overdose of XOFLUZA should consist of general supportive measures, including monitoring vital signs and observing the clinical status of the patient. There is no specific antidote for an XOFLUZA overdose, and it is unlikely to be significantly removed by dialysis, because it is highly protein bound (Prescribing Information for XOFLUZA, 2021; Poisindex, 2021).

Overall, treatment with XOFLUZA is well tolerated. If accidentally ingested, the greatest potential for injury is diarrhea, nausea, and headache. For these reasons, Health Sciences Staff does not think there is a substantial likelihood that XOFLUZA will cause serious injury or death upon acute exposure by a child under 5 years old.

Staff concludes that the Commission may find that the "lack of toxicity and lack of adverse human experience for the substance" is such that the special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 CFR §

[8] [redacted]

[9] The adverse events are: diarrhea, bronchitis, nasopharyngitis, nausea, sinusitis, increase in the level of AST, headache, vomiting, dizziness, leukopenia, and constipation.

[10] The FDA Adverse Event Reporting System (FAERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses FAERS to monitor for new adverse events and medication errors that might occur with these marketed products.

1702.17(a). Staff recommends that the Commission grant the petition to exempt XOFLUZA from special packaging requirements in packages containing not more than 80 mg of the drug, based on this lack of toxicity. It is written as not more than 80 mg of XOFLUZA so that the regulation will cover any dosage level from 80 mg and below.

B. Injury Data

The Division of Epidemiology searched CPSRMS and NEISS databases, and reviewed FDA reports related to adverse events associated with XOFLUZA.

CPSC staff found no incidents related to XOFLUZA in CPSRMS[11] or NEISS[12] from January 2015 through December 2020.

CPSC staff also reviewed 12 reports received from FDA related to AEs associated with XOFLUZA. Of the 12 reports, five involved XOFLUZA use only. Of these five incidents, two reported adverse effects. One patient experienced hallucination, fever, sore throat, and the other patient had cardiac failure. Both were unrelated to XOFLUZA. Six incidents involved multiple drug use and were considered out of scope, and one was a duplicate.

C. Packaging Analysis

Laboratory Sciences staff analyzed the technological feasibility, practicability, and appropriateness of the XOFLUZA packaging. Staff concludes that Genentech's special packaging for XOFLUZA is technically feasible, practicable, and appropriate at all production levels. The firm's XOFLUZA packaging is of a type listed in ASTM D3475-20 and has a certificate of compliance that meets the PPPA requirements. Therefore, it is technologically feasible. The firm's special packaging is adaptable to mass production, and therefore, it is practicable at the current production level. Since the production capacity of the XOFLUZA special packaging is approximately three to five times lower than some other technologically feasible special packaging designs, staff concludes those other designs are potentially more practicable at higher production levels. However, the firm did not provide information of the production capability during an epidemic, or the production capability at the [redacted] site. The firm also did not specify the effects on demand due to government stockpiling. Staff cannot conclude that XOFLUZA special packaging is not practicable at some unidentified higher production level and with production expanded to the

[11] Staff searched the CPSC databases of CPSRMS. These reported deaths and incidents are not a complete count of all that occurred during this period. However, they do provide a minimum number of deaths and incidents occurring during this period. Staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "XOFLUZA."

[12] NEISS injury data are gathered from emergency departments of hospitals selected as a probability sample of all U.S. hospitals with emergency departments. The surveillance data gathered from the sample hospitals enable the CPSC staff to make timely national estimates of the number of injuries associated with specific consumer products. Staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "Xofluza."

[redacted], as the petitioner contends. Finally, the packaging materials in contact with XOFLUZA are approved by the FDA. Therefore, the packaging is appropriate.

Staff concludes that the petitioner has not demonstrated that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA, and therefore, granting the petition request for an exemption on that basis is not justified under 16 CFR § 1702.17(b).

D. Economic Information

The Directorate for Economic Analysis preliminarily concluded that the CRP exemption for XOFLUZA would not have a significant impact on a substantial number of small firms, regardless of whether the petition is granted. However, if Genentech relocates packaging for XOFLUZA to [redacted], it could potentially result in some minor negative impacts for small domestic firms. Therefore, staff requests public comment on any small business impacts that might result.

The petitioner indicates "XOFLUZA is currently packaged at a [redacted] facility in [redacted], which has the equipment necessary to manufacture packaging that meets the Commission's child resistant packaging requirements."[13] Therefore, the petitioner has effectively indicated that it is feasible and practicable to package XOFLUZA in special packaging that meets U.S. requirements. However, Genentech wants to consolidate its production at a facility in [redacted], and the petitioner states in the petition that "requiring special packaging for XOFLUZA may hamper Genentech's ability to respond quickly and efficiently to an increased demand for the drug."[14] According to Genentech, the facility in [redacted] lacks the capability to manufacture special packaging needed to meet *U.S.* child-resistant packaging requirements, adding that "[i]t is not feasible or practical to modify the [redacted] site in a way that would allow Genentech to package XOFLUZA in child-resistant packaging in the quantities that are required."[15] However, the petitioner has not provided sufficient data or evidence to support this claim.

Data needed to evaluate the petitioner's claim might include, at a minimum, the estimated costs of CR packaging and the estimated costs of non-CR packaging. The petitioner did not provide cost estimates for machinery used in automated packaging processes to be purchased, modified, or adapted for CR packaging production.

High-quality CR packaging for pharmaceuticals is available in a variety of locations and forms for firms to scale production. Staff found four firms that provide high-quality CR blister packaging in the [redacted], and one in [redacted]. At present, staff finds it reasonable that it is both technologically feasible and practicable to provide CR packaging from materials and equipment available in the United States and abroad. Staff cannot conclude that requiring special packaging for XOFLUZA would hamper the firm's ability to respond quickly and efficiently to an increase in demand.

[13] Covington & Burling, LLP, March 30, 2020.
[14] Covington & Burling, LLP, March 30, 2020.
[15] Covington & Burling, LLP, March 30, 2020.

III. Options

1. Grant the petition and propose a rule to exempt XOFLUZA from special packaging requirements in packages containing not more than 80 mg of the drug.

The Commission may grant the petition and issue a notice of proposed rulemaking if it preliminarily concludes that exempting XOFLUZA from child-resistant packaging requirements at this level will not present a risk of serious personal injury or illness to children. 16 CFR § 1702.17(a).

2. Deny the petition.

The Commission may deny the petition if it concludes that there is insufficient evidence to show that XOFLUZA at this level would not be hazardous to children.

3. Defer the petition.

The Commission may defer the petition if it concludes that more information on XOFLUZA is needed to decide.

IV. Staff Conclusions and Recommendation

Staff concludes that CRP is not necessary for XOFLUZA tablets in packages containing not more than 80 mg of the drug because of low acute toxicity and the lack of serious adverse human experience data associated with acute ingestion. Therefore, because of the lack of toxicity and lack of adverse human experience for the substance, special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 CFR § 1702.17(a). Based on the above analysis, staff recommends that the Commission: (1) grant the petition; and (2) publish an NPR to exempt XOFLUZA from the CRP requirement of the PPPA.

V. References

Dziewiatkowski N.A., Osmon E.N., Chahine E.B., Thornby K.A. (2019). Baloxavir: a novel single-dose oral antiviral for the treatment of influenza. Sr Care. Pharm; 34:243-52.
Hayden F.G. (2018). Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. The New England Journal of Medicine.379:(10).

Heo Y-A. (2018). Baloxavir: First Global Approval. Drugs 78:693-697.

Hirotsu N. (2019). Baloxavir Marboxil in Japanese Pediatric Patients with Influenza: Safety and Clinical and Virologic Outcomes. Clinical Infectious Diseases Clin Infect Dis Aug 14;71(4):971-981.

https://clinicaltrials.gov/ct2/show/NCT03653364

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210854Orig1s000medR.pdf

https://www.gene.com/download/pdf/xofluza_prescribing.pdfMicromedex Solutions, Poisindex XOFLUZA search 2/1/2021.

Taieb V., Ikeoka, Fang-Fang Ma H., Borkowski K., Aballea S., Tone Keiko and Hirotsu N. (2019). A network meta-analysis of the efficacy and safety of baloxavir marboxil versus neuraminidase inhibitors for the treatment of influenza in otherwise healthy patients. Current Medical Research and Opinion 35:8, 1355-1364.

TAB A: PETITION FOR EXEMPTION FROM SPECIAL PACKAGING REQUIREMENT (For Official Use Only) REMOVED

TAB B: Toxicity Review of XOFLUZA™

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

Date: September 1, 2021

To: Cheryl Scorpio, Ph.D.,
Pharmacologist, Project Manager
Division of Pharmacology and Physiology Assessment
Directorate for Health Sciences

Through: Mary Kelleher
Associate Executive Director
Directorate for Health Sciences

Stefanie Marques, Ph.D.,
Director, Division of Pharmacology and Physiology Assessment
Directorate for Health Sciences

From: Adrienne Layton, Ph.D.,
Pharmacologist, Division of Pharmacology and Physiology Assessment
Directorate for Health Sciences

Subject: Toxicity Review of XOFLUZA™

Introduction

This memorandum describes the toxicity of XOFLUZA™ based upon National Electronic Injury Surveillance System (NEISS),[16] Consumer Product Safety Risk Management System (CPSRMS),[17] U.S. Food and Drug Administration (FDA), FDA Adverse Event Database (FAERS), New Drug Application (NDA), the medical literature, clinicaltrials.gov, and the XOFLUZA Prescribing Information, 2021. Staff concludes that the "lack of toxicity and lack of adverse human experience for the substance" is such that the special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 CFR § 1702.17(a).

[16] NEISS injury data are gathered from emergency departments of hospitals selected as a probability sample of all U.S. hospitals with emergency departments. The surveillance data gathered from the sample hospitals enable the CPSC staff to make timely national estimates of the number of injuries associated with specific consumer products. Staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "XOFLUZA."

[17] Staff searched the CPSRMS databases. These reported deaths and incidents are not a complete count of all that occurred during this period. However, they do provide a minimum number of deaths and incidents occurring during this period. Staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "XOFLUZA."

Influenza Viruses

Influenza viruses can be subdivided into three distinct influenza types: A, B, and C.[18] Only influenza types A and B are considered pathogenic in humans, because influenza C virus does not cause significant disease.

Due to a lack of proofreading[19] activity, influenza viruses have a high gene mutation rate, resulting in approximately one error per replicated genome (Drake, 1993). Mutations occur during viral replication (Uehara et al., 2020).

Annual epidemics are a result of evolution of the surface antigens of influenza A and B virus (antigenic drift), while pandemics are a result of novel viral subtypes of influenza A created by reassortment of the segmented genome (antigenic shift). Eventually these proteins on the viral particles become sufficiently different such that host antibodies are unable to neutralize the virus. Antigenic shift occurs less frequently than antigenic drift and is caused when two different viruses, possibly each from a different host species, coinfect a single host which becomes a "mixing vessel."

Currently, XOFLUZA is marketed in tablet form and dispensed in child-resistant packaging (CRP). A patient must take XOFLUZA within 48 hours of symptom onset for it to be effective. The drug can be taken with or without food, but it should not be taken with calcium-containing compounds (*e.g.*, dairy products, calcium-supplemented beverages, laxatives containing polyvalent cations, antacids, or oral supplements containing calcium, iron, magnesium, selenium, or zinc) because these compounds inhibit its potency. An influenza lifecycle is shown in Figure 1. Dosing of XOFLUZA is shown in Table 1.

[18] The groups are based on serology.

[19] Proofreading is the process whereby DNA polymerases, the enzymes that build DNA in cells**,** check each base that they add during DNA synthesis.

Figure 1. Life Cycle and Potential Role of Endonuclease Inhibition and Other Targets in the Treatment of Influenza.

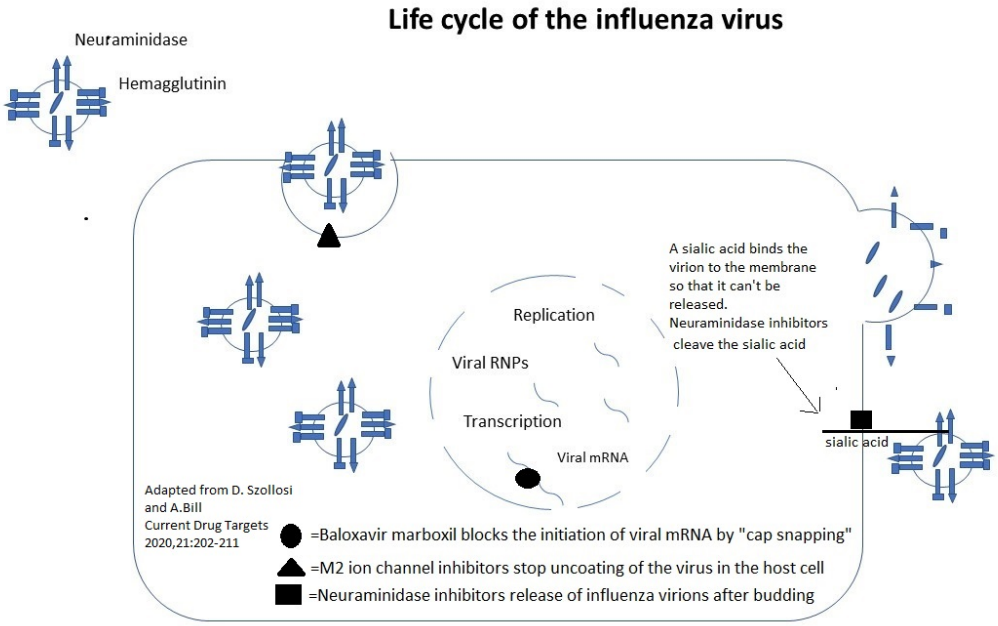

Table 1. Dosing Regimen of XOFLUZA in Adults and Children with Uncomplicated Influenza[20]

Patient Body Weight (kg)	Recommended Single Oral Dose in Patients 12 Years of Age and Older
Less than 80 kg	One 40 mg tablet (blister card contains one 40 mg tablet)
At least 80 kg	One 80 mg tablet (blister card contains one 80 mg tablet)
	Recommended Single Oral Dose (Suspension)
Less than 80 kg	40 mg/20ml (1 bottle), taken as a single dose[21]
At least 80 kg	80 mg/20ml (2 bottles), taken as a single dose

Source: Prescribing Information for XOFLUZA, 2021

[20] Uncomplicated influenza illness is typically characterized by the abrupt onset of upper respiratory tract signs and symptoms (*e.g.*, fever, chills, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis). Infection complications can result in severe disease. In young children, complications that can occur include otitis media and respiratory (*e.g.*, croup, bronchiolitis, tracheitis), cardiac (myocarditis and pericarditis), musculoskeletal (severe myositis), and neurologic (encephalopathy, encephalitis, transverse myelitis, and acute disseminated encephalomyelitis), (CDC 2020).

[21] Each bottle contains 40 mg in a 20 ml volume when constituted resulting in a final concentration of 2 mg/ml.

Pharmacokinetics of XOFLUZA

XOFLUZA is a prodrug, a biologically inactive compound, bioactivated upon administration through enzymatic or chemical reactions within the body. This releases the parent compound to elicit its pharmacological response (Najjar, 2019). The pharmacokinetics for XOFLUZA were similar for otherwise healthy adults and adolescents and those at high risk of developing influenza-related complications. The pharmacokinetics of XOFLUZA in humans is shown below.

Table 2. The Pharmacokinetic Profile of XOFLUZA

ABSORPTION	
T max (hours)	4
Effect of food (relative to fasting)	C_{max} down 48%, AUC down 36%
DISTRIBUTION	
% bound to human serum proteins	92.9% - 93.9%
Ratio of blood cell to blood	48.5% - 54.4%
Volume of distribution (V/F, liters)	1180 (20.8%)
ELIMINATION	
Major route of elimination	Metabolism
Clearance (CL/F)(liters/hour)	10.3 (22.5%)
Half-life (hours)	79.1 (22.4%)
METABOLISM	
Metabolic pathways	UGT1A3[22], CYP3A4[23]
EXCRETION	
% of dose excreted in urine	14.7 (Total radioactivity), 3.3 (XOFLUZA)
% of dose excreted in feces	80.1 (Total radioactivity)

Source: Prescribing information for XOFLUZA 2021,12.3 CLINICAL PHARMACOLOGY.

Pre-clinical Toxicology Review of XOFLUZA Animal Studies

The pre-clinical toxicology studies included in this section are based on the toxicology report and information required by the FDA for an Investigational New Drug Application (IND) or a New Drug Application (NDA) for XOFLUZA (FDA 2018). The following animal toxicological data provided a starting point for staff to identify potential toxicity from XOFLUZA in humans.

Toxicity endpoints evaluated for XOFLUZA include genotoxicity, phototoxicity, safety pharmacology, repeat dose (2 weeks, 1 month, juvenile 40 days), and reproductive and

[22] UDP-glucuronosyltransferase 1-3 is an enzyme that in humans is encoded by the ***UGT1A3*** gene.
[23]CYP3A4 is an enzyme, mainly found in the liver and intestine. It oxidizes small foreign organic molecules, such as toxins or drugs, so that they can be removed from the body.

developmental toxicity. The sponsor conducted all animal studies by following International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Results for genotoxicity were negative for all studies. Phototoxicity was positive *in vitro* and negative *in vivo*. No single-dose acute studies were reported. GI effects (loose stools, diarrhea, and vomiting) were observed in the monkey cardiovascular safety pharmacology study at the lowest dose tested (200 mg/kg). The NOAEL of 100 mg/kg was based on decreases in body weight and food intake, as well as increases in abortions and skeletal effects in a rabbit embryonic fetal development study. Subacute studies (2 weeks) in monkeys, rats, and rabbits were available. In a 1-month study in rats, the NOAEL of 20 mg/kg-d was based on liver, platelet, clotting factor, and thyroid effects. In a 1-month study in monkeys, the NOAEL of 10 mg/kg-d was based on liver and thyroid effects (FDA, 2018). See Appendix A for more details of the XOFLUZA animal studies.

XOFLUZA Clinical Trials

Summary of Clinical Trials

Clinical research refers to studies, or trials, that are performed in human subjects. Five major clinical trials relevant to this petition were conducted for XOFLUZA and are shown in Table 3. No significant health effects following XOFLUZA administration are noted in the CAPSTONE 1 and CAPSTONE 2 clinical trials. There is no demonstration of significant toxicity following XOFLUZA administration in the medical literature. Deaths reported from the FDA following XOFLUZA treatment are not related to XOFLUZA or do not have sufficient information related to deaths to draw a conclusion. In addition, none of the reported SAEs[24] were related to XOFLUZA treatment in the FDA reviewer's opinion. Table 4 is a summary of the adverse health effects observed in the clinical trials. See Appendix B for more details regarding toxicity in the XOFLUZA clinical trials.

[24] An SAE is a serious adverse event.

Table 3. Major Clinical Trials of XOFLUZA Relevant to this Petition

Status	NCT[25] number	Sponsor	Drugs	Study population	Actual or estimated study completion date
Completed	NCT02954354 (CAPSTONE 1),	Shionogi	Xofluza Oseltamivir Placebo	Influenza patients 12 - 64 years old	April 24, 2017
Completed	NCT02949011 (CAPSTONE 2)	Shionogi	Xofluza Oseltamivir Placebo	Patients with influenza at high risk of influenza complications ≥ 12 years old	April 20, 2018
Completed	NCT03653364	Hoffman-La Roche	Xofluza	Healthy pediatric patients from birth to <1 year with influenza-like symptoms	May 23, 2020
Completed	NCT03629184 (MiniSTONE-2)	Hoffman-La Roche	Xofluza Oseltamivir	Healthy pediatric patients 1 to <12 years old with influenza-like symptoms	June 19, 2020
Completed	NCT03684044 (BLOCKSTONE)	Hoffman-La Roche	Xofluza Placebo	Hospitalized participants with severe influenza ≥ 12 years old	January 6, 2021

Source: ClinicalTrials.gov

[25] National Clinical Trial (NCT) is an identifier assigned by the National Library of Medicine.

Table 4: Percentage of Subjects with Adverse Events Reported in Subjects who Received XOFLUZA in Clinical Trials[26]

Adverse Event	XOFLUZA™ (N= 710)	Placebo (N= 409)
Diarrhea	3%	5%
Bronchitis	3%	4%
Nasopharyngitis	1%	1%
Nausea	2%	3%
Headache	1%	1%
Sinusitis	2%	3%

Source: XOFLUZA Prescribing Information, 2021

Deaths and Serious Adverse Events Associated with XOFLUZA Clinical Trials

No deaths were reported in the original NDA submission of XOFLUZA to the FDA**.**
A single death was reported in the Safety Update Report (SUR) for a 66-year-old patient of Trial 1602T0832 in the NDA.[27] This trial included high-level safety results comparing XOFLUZA, placebo, and oseltamivir in the treatment of influenza in subjects at high risk of influenza complications. The death of the 66-year-old male was judged as not related to XOFLUZA because the subject's symptoms began before he was given the study drug. The FDA reviewer agreed that his death was not related to XOFLUZA. Deaths following Xofluza treatment from The FDA Adverse Event Reporting System (FAERS) are shown in Table 5.

Table 5. Deaths Reported from the FDA FAERS System

AERS document number	Narrative	Conclusion
AER 2276694	A 23-year-old male died while being treated with XOFLUZA, Ciprofloxacin, carbocisteine, and acetaminophen.	Death was unrelated to the XOFLUZA treatment.
AER 2295819	A 63-year-old female patient	The cause of death is unknown. There is insufficient information reported on this case to perform a meaning assessment.

[26] Trial 1518T0821, a Phase 2 dose-finding trial, was conducted in Japan, in subjects from 20 to < 65 years of age. Trial 1601T0831, the Phase 3 safety and efficacy trial, differed from 1518T0821 in what subjects were enrolled in Japan, the U.S., and Canada, and 1601T0831 enrolled subjects from 12 to < 65 years of age.

[27] An arm of CAPSTONE 1.

AER2301879	An 82-year-old male died while being treated with XOFLUZA.	The cause of death is unknown.[28]
AER 2304921	A 48-year-old who also had diabetes, high blood pressure, and influenza A was treated with XOFLUZA and died.	The physician assessed the death as not related to XOFLUZA.
AER 2279720	An 89-year-old male died while being treated with XOFLUZA and Peramivir.	The cause of death is unknown.

Source: https://open.fda.gov/data/faers.

A "serious adverse event" (SAE) was defined by the sponsor as one that caused interruption of the subject's daily activities or had a clinically significant effect. The following data in this section are from FDA in 2018.

No SAEs were reported in any of the 11 Phase 1 studies or in the Phase 2 trial (1518T0821[29]). Eight SAEs were reported in six subjects (0.7%) who received XOFLUZA in the Phase 3 trial, (1601T0831), along with four subjects who received placebo (1%) and one who received oseltamivir (0.2%). The eight SAEs reported in subjects who received XOFLUZA were diarrhea, nausea, vomiting, viral meningitis, otitis media, polydipsia,[30] headache, and incarcerated inguinal hernia. All, except for the inguinal hernia, occurred during the 6 days after treatment with XOFLUZA; five occurred within 2 days of receiving XOFLUZA (diarrhea, nausea, vomiting, polydipsia, and otitis media). Diarrhea, nausea, vomiting, and polydipsia were judged as treatment related. The incarcerated inguinal hernia[31] was reported on Day 8. The viral meningitis occurred in a 24-year-old male who received a single 40 mg dose of XOFLUZA on Day 1; he experienced fever on Days 3 and 6, and he presented to the emergency department with headache, nausea, and vomiting. The FDA reviewer reported that the viral meningitis[32] may represent progressive influenza, complicated by influenza meningitis.

SAEs occurred in the Phase 3 trial (CAPSTONE 1) at equivalent levels between the treatment groups (5, 9 and 8 subjects (all at 1%), in the XOFLUZA, placebo, and oseltamivir treatment groups, respectively). The FDA reviewer opined that none of the SAEs were related to their XOFLUZA treatment.

Overall psychiatric AEs were uncommon in these trials, and none were increased in the XOFLUZA treatment groups compared to control groups. The most frequently reported neurologic AE was headache, which is a common symptom in patients with influenza. Therefore, the FDA reviewers did not indicate that the SAEs above were related to XOFLUZA toxicity.

[28] There is insufficient information reported to Genentech on this case to perform a meaning assessment.
[29] An arm of CAPSTONE 1.
[30] Abnormal thirst.
[31] An incarcerated inguinal hernia is a hernia that becomes stuck in the groin or scrotum and cannot be massaged back into the abdomen.
[32] *Aseptic meningitis* is an illness characterized by serous inflammation of the linings of the brain (*i.e*., *meninges*) accompanied by headache and fever.

Clinical trials and Adverse Events for Children

The FDA concluded there are no concerning safety findings for children from Phase 1, Phase 2, or Phase 3 trials of XOFLUZA. A total of 117 children (8% of all subjects) were enrolled in Trial 1601T0831 and randomized to either XOFLUZA (N=76) or placebo (N=41) treatment groups. A total of 107 subjects were randomized: 105 in the age 2- to 12-year-old cohort and two subjects in the 6 months to < 2 years old cohort. Adverse events reported from trial 1601T0831 are shown in Table 6 below.

Table 6. Adverse Events Reported with at Least 2 Adolescents in Either Arm in Trial 1601T0831

	XOFLUZA N=76	**Placebo N=41**
Subjects with any AE	13 (17%)	14 (34%)
Diarrhea	3 (4%)	2 (5%)
Bronchitis	1 (1%)	2 (5%)
Otitis media	0	2 (5%)
Nightmares	0	2 (5%)
Headache	1 (1%)	2 (5%)

Source: FDA Clinical Report of Xofluza Application 210854Orig1s000.

Case Studies of XOFLUZA from the Medical Literature

Because there is a lack of significant toxicity in the clinical trial data, staff searched the medical literature for any adverse effect data following XOFLUZA dosing. There are only five cases of patients dosed with XOFLUZA in the medical literature. The cases do not demonstrate any significant toxicity directly related to XOFLUZA, as shown below in Table 7.

Table 7. Case Studies from the Medical Literature

Narrative	Reference
An immunocompromised 49-year-old male patient was diagnosed with upper tract influenza A virus infection. He was initially given oseltamivir, peramivir. He was then given XOFLUZA. The symptoms resolved and the influenza diagnostic test became negative.	(Harada et al., 2020)

A 34-year-old male with infantile paralysis presented at a clinic 5 days previously with high fever and was diagnosed with influenza A. Oral XOFLUZA was administered. He improved, and his fever went down 2 days later.	(Seki et al., 2019).
A 22-year-old female with a history of asthma, diabetes, and kidney disease presented with cough and congestion of 3 days' duration. She was given XOFLUZA. Chest x-rays taken 48-hours post initiation of XOFLUZA showed significant improvement. She was extubated, and was subsequently discharged home.	(Tobar Vega et al., 2020)
XOFLUZA was administered to a 62-year-old female. She exhibited ischemic colitis, which resolved on Day 8.	(Kanai et al., 2019)
XOFLUZA further increased a clotting time in a 45-year-old male taking warfarin. This was a modification to a laboratory not an adverse effect.	(Kurosawa et al., 2021).

Summary

[redacted]. XOFLUZA also has been studied in pediatric patients (Hirotsu, 2019; Heo, 2018; NCT03653364, CAPSTONE 2; Hayden, 2018; Dziewiatkowski et al., 2019). Overall, clinically relevant doses of XOFLUZA, (40 or 80 mg total dose), in humans are well tolerated (Dziewiatkowski et al.,2019; Taieb et al., 2019; Ng, 2019; Hayden, 2018).

The analysis of total AEs included 10 studies with six treatments and 5628 patients. AE did not differ significantly between placebo and XOFLUZA. For drug-related vomiting, 3297 patients from five studies were included. XOFLUZA did not differ from placebo in these studies. (Taieb et al., 2019). Any adverse event[34] (of 610 patients (12 to 64 years old) in the CAPSTONE 1 clinical trial was 1.0% grade 3 or grade 4, which can be categorized as not serious. Five deaths have been reported by the AERs System; however, these deaths have been determined not to be related to XOFLUZA.

The most common AE of the correct dose of XOFLUZA was diarrhea (Heo, 2018; Shionogi prescribing info). The XOFLUZA Product Information, 2021 reported that diarrhea (3%), bronchitis (3%), nausea (2%), headache (1%) were the most significant adverse events found

[33] [redacted]

[34] The adverse events are: diarrhea, bronchitis, nasopharyngitis, nausea, sinusitis, increase in the level of AST, headache, vomiting, dizziness, leukopenia, and constipation.

No incidents of poisoning have been reported in NEISS or CPSRMS from January 2005 through December 2020. No AEs directly related to XOFLUZA from the FDA Adverse Event Reporting System (AERS) were identified.

Treatment of an overdose of XOFLUZA should consist of general supportive measures, including monitoring of vital signs and observations of the clinical status of the patient. There is no specific antidote for overdose with XOFLUZA, and it is unlikely to be significantly removed by dialysis because it is highly protein bound (Prescribing Information for XOFLUZA, 2021; Poisindex, 2021).

Health Sciences Conclusion

Overall, treatment with XOFLUZA is well tolerated. If accidentally ingested, the greatest potential for injury is diarrhea, nausea, and headache. For these reasons, Health Sciences staff does not think there is a substantial likelihood that XOFLUZA will cause serious injury or death upon acute exposure by a child under 5 years old.

Staff concludes that the "lack of toxicity and lack of adverse human experience for the substance" is such that the special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 CFR § 1702.17(a).

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Appendix A. XOFLUZA Animal Studies

The pre-clinical toxicological information in this section was obtained from the FDA nonclinical review and evaluation of XOFLUZA New Drug Application Pharmacology/Toxicology NDA/BLA. Genentech conducted the research and submitted the data to the FDA, which reviewed the data, and made conclusions.

XOFLUZA tested negative in all genotoxicity[35] studies. Carcinogenicity studies have not been conducted (FDA, 2018).

In preclinical safety studies, including cardiac electrophysiology, at twice the expected exposure from the recommended dosing, XOFLUZA did not prolong the QT interval. The experimental details are not available (FDA, 2018).

FDA determined that XOFLUZA has phototoxic potential. XOFLUZA tested positive for phototoxicity at 0.1 and 0.02 (weight percent by volume) in an *in vitro* test using sheep red blood cells. The skin phototoxicity study in mice revealed no phototoxicity *in vivo* (FDA, 2018).

Standard acute toxicity or LD_{50} studies with XOFLUZA have not been conducted. In a cardiovascular safety pharmacology study, monkeys were treated with a single dose of XOFLUZA (0, 200, 400 mg/kg) by the oral route. GI effects (loose stools, diarrhea, and vomiting) were observed when tested (FDA, 2018).

Sprague-Dawley rats were treated daily with XOFLUZA (0, 20, 200, 2000 mg/kg) (10 animals per sex/dose) by the oral route for 2 weeks. Increased liver weights and thyroid hyperplasia were noted at the mid and high doses. Increased serum prothrombin time (PT) and activated partial thromboplastin time (APTT) were observed at the mid and high doses (FDA,2018).

New Zealand rabbits were treated daily with XOFLUZA (0, 100, 300, 1000 mg/kg) by the oral route for 2 weeks. Decreases in body weight and food consumption, and GI effects (abnormal stool color) were noted at the high dose (FDA, 2018).

Cynomolgus monkeys were treated daily with XOFLUZA (0, 20, 60, 200 mg/kg-d) by the oral route for 2 weeks. Sporadic vomiting occurred at the high dose 1 or 4 hours after dosing from dose day 4 until the end of the dosing period. The GI effects in monkeys (loose stools, diarrhea, and vomiting) at dose of 200 mg/kg were confirmed by the sponsor (petition p. 10). In addition to the GI effects, increases in hepatic enzyme serum levels were noted for all doses on days 7 and 14. In another monkey oral 2-week study, with lower doses (0, 3, 10 mg/kg, daily), similar increases in serum hepatic enzymes (AST,[36] ALT,[37] and GLDH[38]) were noted at the 3 mg/kg-d dose (FDA, 2018).

Rats were treated daily with XOFLUZA (0, 20, 200, 2000 mg/kg) by the oral route for 1 month. Increased serum levels of platelets, PT and APTT were observed at some mid and high doses. A

[35] Property of chemical agents that damage genetic information causing cell mutations.
[36] AST (aspartate aminotransferase) is an enzyme found mostly in the liver and muscles. When the liver is damaged, it releases AST into the bloodstream.
[37] ALT (alanine aminotransferase) is an enzyme normally present in liver and heart cells that is released into the bloodstream when the liver or heart is damaged.
[38] GLDH is an enzyme can be measured in a medical laboratory to evaluate liver function.

No Observed Adverse Effect Level (NOAEL) of 20 mg/kg was established by the FDA based on the study findings in liver (changes in organ weights, histopathology, and serum chemistry), platelet levels, clotting-factor levels, and thyroid effects at the mid and high doses. The thyroid effects observed in rats resolved during recovery (FDA, 2018).

Monkeys were treated daily with XOFLUZA (0, 1, 10, 100 mg/kg) by the oral route for 1 month. The FDA established a NOAEL of 10 mg/kg, based on the study findings in liver (changes in organ weights and serum chemistry) at the high dose, and in thyroid effects at the mid and high doses. Increased thyroid weight in males at the high dose was observed at the end of dosing and remained elevated through the recovery period (FDA, 2018).

Juvenile rats were treated daily with XOFLUZA (0, 100, 300, or 1000 mg/kg) by the oral route for 40 days (PND10 to 49). FDA established a NOAEL of 1000 mg/kg. Increased APTTs were observed at the mid and high doses in male rats in the juvenile study (FDA, 2018).

Male and female rats were dosed daily with XOFLUZA (0, 20, 200, 1000 mg/kg) by the oral route. Males were dosed for 4 weeks before mating, throughout the mating period, and necropsy was conducted at 14 weeks old. Females were dosed for more than 2 weeks before the mating period, throughout the mating period, until gestation day (GD) 13. Several male and females dosed at 1000 mg/kg had abnormally colored feces due to the undigested drug. The FDA established a NOEAL of 1000 mg/kg (FDA, 2018).

Pregnant rats were dosed with XOFLUZA (0, 20, 200, 1000 mg/kg) by once daily oral gavage on GD 6 through GD 17. All animals were observed until GD 21. The FDA established a NOAEL of 1000 mg/kg (FDA, 2018).

Pregnant rabbits were dosed with XOFLUZA (0, 30, 100, 1000 mg/kg) once daily by oral gavage on GD[39] 7 to 19. Dams were euthanized on GD 28. The FDA established a NOAEL of 100 mg/kg, based on decreases in body weight and food intake, abortions, and fetal skeletal effects at the high dose (FDA,2018). Similar side effects were observed in a rabbit embryonic fetal development range-finding study and with an FDA determined NOAEL of 100 mg/kg (FDA, 2018).

Pregnant rats were dosed daily with XOFLUZA (0, 20, 200, 1000 mg/kg) by oral route from GD 6 to postnatal day 20. Dams were necropsied at weaning. The FDA established a NOAEL of 1000 mg/kg (FDA, 2018).

[39] GD is the number of days between conception and birth.

Appendix B. XOFLUZA Clinical Trials

The data in this appendix are from the FDA Center for Drug Evaluation and Research Evaluation (CDER).[40]

CAPSTONE 1

CAPSTONE 1 is a phase 3 clinical trial where XOFLUZA was studied in 1,436 adults and adolescents ages 12 to 64 years old weighing at least 40 kg with signs of influenza. Patients received XOFLUZA,[41] or placebo, once on day 1, oseltamivir twice a day for 5 days. The primary endpoint of the trial was alleviation of symptoms,[42] defined as the time when all symptoms, self-assessed by each patient twice per day, was none or mild at least 21.5 hours (XOFLUZA Prescribing Information, 2021). XOFLUZA treatment was associated with rapid declines in infectious viral load, compared to placebo, or oseltamivir treatments. The median time to alleviate symptoms was shorter in the XOFLUZA treatment group for both adolescents (38.6 hours) and adults (25.6 hours) (Ng, 2019).

Treatment Emergent Adverse Events

Table 1 displays all AEs reported in at least 1 percent of subjects who received XOFLUZA in the CAPSTONE 1 Phase 3 clinical trial (CAPSTONE 1) and was obtained from the medical literature. This analysis only includes subjects who were exposed to the to-be-marketed doses of 40 mg and 80 mg. There were no treatment-emergent AEs reported in more than 5 percent of subjects in any of the trials. Note that the sponsor defined an "adverse drug reaction" as one that: (1) was reported in at least 2 percent of subjects who received XOFLUZA, (2) occurred at a higher incidence than the placebo treatment group, and (3) was attributed to the study drug by the investigator.

[40] htpps://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210854Orig1s000medR.pdf.

[41] weight adjusted 80mg for 80Kg and above. 40 mg for those who weighed 40 to < 80 kg.

[42] A moderate or severe respiratory symptom (Cough, nasal congestion, sore throat), or a moderate or severe systemic effect (headache, feverish or chills, muscle or joint pain or fatigue).

Table 1. Number of Subjects with Treatment-Emergent Adverse Events Reported in 1% or More of Subjects Who Received XOFLUZA

	CAPSTONE 1		
	XOFLUZA N=610	**Placebo N=309**	**Oseltamivir N=513**
Headache	4 (1%)	6 (1%)	4 (1%)
Dizziness	3 (0.4%)	6 (1%)	1 (0.2%)
Dysgeusia[43]	2(0.3%)	0 (0%)	0 (0%)
Hypoesthesia[44]	1 (0.1%)	0 (0%)	0 (0%)
Parosmia[45]	1 (0.1%)	0 (0%)	0 (0%)
Syncope[46]	1 (0.1%)	0 (0%)	0 (0%)
Migraine	0 (0%)	0 (0%)	1 (0.2%)

Source: Hayden, 2018

The AEs reported in the XOFLUZA treatment groups were diarrhea and bronchitis. It is also worth noting that diarrhea is reported more frequently in the placebo treatment group than the drug treatment group (XOFLUZA Prescribing Information, 2021).

AEs were reported in 20.7 percent of XOFLUZA recipients, 24.6 percent of placebo recipients, and 24.8 percent of oseltamivir recipients (Hayden, 2018). AEs associated with cessation of this trial occurred in various groups. Two serious AEs, involving an incarcerated inguinal hernia and a case of aseptic meningitis, were noted in the XOFLUZA group, but neither case was considered to be related to the trial regimen. AEs related to the trial regimen were 4.4 percent, while it was 3.9 percent in the placebo group (Hayden, 2018.). AEs in one arm of the CAPSTONE 1 are shown below in Table 2.

[43] Dysgeusia is a distortion of the sense of taste.
[44] Hypoesthesia is numbness.
[45] Parosmia is the loss of scent intensity.
[46] Syncope is a temporary loss of consciousness due to a fall in blood pressure.

Table 2. Adverse Events from Arms of the CAPSTONE 1 Clinical Trial

	Xofluza (N=610)		**Placebo (N=309)**	
	Any grade	Grade 3[47] or 4[48]	Any grade	Grade 3 or 4
Any adverse event	126 (20.7)	6 (1.0)	76 (24.6)	4 (1.3)
Adverse events reported in >1% of patients in any group				
Diarrhea	18 (3.0)	1 (0.2	14 (4.5)	1 (0.3)
Bronchitis	16 (2.6)	0	17(5.5)	1 (0.3)
Nasopharyngitis	9 (1.5)	0	2 (0.6)	0
Nausea	8 (1.3)	1 (0.2)	4 (1,3)	1 (0.3)
Sinusitis	7 (1.1)	0	8 (2.6)	1 (0.3)
Increase in ALT level	6 (1.0)	0	4 (1.3)	0
Headache	5 (0.8)	1 (0.2)	3 (1.0)	0
Vomiting	5 (0.8)	1 (0.2)	2 (0.6)	0
Dizziness	3 (0.5)	0	4 (1.3)	0
Leukopenia	0	0	3 (1.0)	0
Constipation	0	0	3 (1.0)	0
Adverse event considered to be related to the trial regimen	27 (4.4)	2 (0.3)	12 (3.9)	1 (0.3)
Adverse events considered to be related to the trial regimen and reported in > 1% of patients in any group				
Diarrhea	11 (1.8)	1 0.2)	4 (1.3)	0
Nausea	2 (0.3)	1 (0.2)	2 (0.6)	1 (0.3)
Serious adverse event	2 (0.3)	2 (0.3)	0	0
Adverse event leading to discontinuation of the trial regimen	2 (0.3)	0	1 (0.3)	1 (0.3)

Source: Hayden et al., 2018.

CAPSTONE 2

CAPSTONE 2 was a double-blind phase III trial that compared XOFLUZA with placebo or oseltamivir in patients at least 12 years old at high risk for influenza complications (Hayden, 2018). The majority of subjects had underlying asthma or chronic lung disease, diabetes, heart disease, morbid obesity, or were 65 years of age or older. The efficacy of XOFLUZA in pediatric patients (ages 12-17 years) with uncomplicated influenza A or B was shown in a single-arm study. Patients received a single dose of XOFLUZA 40 or 80 mg XOFLUZA. Adverse

[47] Grade 3 from the Common Criteria Terminology for Adverse Events of the Department of Health and Human Services, (Version 4.0) refers to Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

[48] Grade 4 from the Common Criteria Terminology for Adverse Events of the Department of Health and Human Services, (Version 4.0) refers to Grade 4 refers to Life-threatening consequences; urgent intervention indicated.

events from CAPSTONE-2 are shown in Table 6. AEs from Trial 1518T0821 and Trial 1601T0831 are shown in Table 3. From the lack of toxicity in the data in the tables below, staff concludes that there is no significant concern about the health effects following XOFLUZA administration in the studies.

Table 3. Adverse Event for XOFLUZA from the CAPSTONE 2 Clinical Trial.

System Organ Class	**N (%)**	**Number of Events Duration of AE[49]:min, max**	**N (%)**	**Number of Events Duration of AE: min, max**
Patients with any AE	37 (34.6)	49 (1, NR)	19 (17.8)	22 (3, NR)
Infections and infestations	14	15 (3 16)	14 (13.1)	15 (3, 16)
Pharyngitis	3	3 (9,12)	3(2.8)	3 (9,12)
Bronchitis	2	2 (8,12)	2 (1.9)	2 (8,12)
Sinusitis	2	2 (8,16)	2 (1.9)	2 (8,16)
Oral Herpes	2 (1.9)	2 (6, 8)	2 (1.9)	2 (6, 8)
Gastroenteritis	1 (0.9)	1 (3)	1 (0.9)	1 (3)
Influenza	1 (0.9)	1 (7)	1 (0.9)	1 (7)
Nasopharyngitis	1 (0.9)	1 (6)	1 (0.9)	1 (6)
Varicella	1 (0.9)	1 (12)	1 (0.9)	1 (12)
Bacterial infection	1 (0.9)	1 (5)	1 (0.9)	1 (5)
Bacterial rhinitis	1 (0.9)	1 (11)	1 (0.9)	1 (11)
Metabolism and nutrition disorders	1 (0.9)	1 (3)	1 (0.9)	1 (3)
Dehydration	1 (0.9)	1 (3)	1 (0.9)	1 (3)
Psychiatric disorders	1 (0.9)	1 (1)	0	0
Nightmare	1 (0.9)	1 (1)	0	0
Nervous system disorders		2 (1,2)	0	0
Headache	2 (1.9)	2 (1,2)	0	0
Respiratory, thoracic, and mediastinal disorders	2 (1.9)	5 (4,46)	3 (2.8)	4 (6, 46)

[49] Duration of AE (days)= (date of outcome) -(date of onset) +1. If the AE did not resolve, or was not resolving until the day of outcome assessment, duration of the AE is defined as NR.

System Organ Class	N (%)	Number of Events Duration of AE[49]:min, max	N (%)	Number of Events Duration of AE: min, max
Upper respiratory Tract inflammation	4 (3.7)	3 (6, 14)	2 (1.9)	3 (6,14)
Epistaxis	1 (0.9)	1 (4)	0	0
Rhinitis allergic	1 (0.9)	1 (46)	1 (0.9)	1 (46)
Gastrointestinal disorders	16 (15)	16 (6)	0	0
Vomiting	8 (7.5)	8 (4)	0	0
Diarrhea	3 (2.8)	3 (46)	0	0
Constipation	2 (1.9)	2	0	0
Dental caries	1 (0.9)	1	0	0
Acetonemic: vomiting	1 (0.9)	1	0	0
Feces soft	1 (0.9)	1	0	0
Skin and subcutaneous tissue disorders	2 (1.9)	2	1 (0.9)	1 (3)
Dry skin	1 (0.9)	1	0	0
Urticaria	1 (0.9)	1	1 (0.9)	1 (3)
Musculoskeletal and connective tissue disorders	2 (1.9)	2	0	0
Back pain	1 (0.9)	1	0	0
Myalgia	1 (0.9)	1	0	0
Instigations	2 (1.9)	3	0	0
Alanine aminotransferase increased	1 (0.9)	1	0	0
Aspartate aminotransferase increased	1 (0.9)	1	0	0
Blood urine present	1 (0.9)	1	0	0
Injury, poisoning, and procedural complications	2 (1.9)	2	1 (0.9)	1 (NR)
Ligament sprain	2 (1.9)	2	1 (0.9)	1 (NR)

Source: Hirotsu, 2019.

TAB C: XOFLUZA™ Related Deaths, Injuries, and Potential Injuries

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

Date: September 1, 2021

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Pharmacologist, Project Manager
Pharmacology and Physiology Assessment
Directorate for Health Sciences

THROUGH : Stephen Hanway
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Directorate for Epidemiology

Risana Chowdhury
Director, Division of Hazard Analysis
Directorate for Epidemiology

FROM : Angie Qin
Statistician
Division of Hazard Analysis
Directorate for Epidemiology

SUBJECT : XOFLUZA™ Related Deaths, Injuries, and Potential Injuries

I. Introduction

The Poison Prevention Packaging Act (PPPA) requires "special packaging" or CRP for certain "household substances," with requirements codified at 16 CFR § 1700 and 16 CFR § 1702.

In March 2020, the U.S. Consumer Product Safety Commission (CPSC) received a petition from Genentech for an exemption from the special packaging requirements of the PPPA for its prescription drug XOFLUZA™ (Baloxavir marboxil). XOFLUZA is a one-dose antiviral medication used for treatment of influenza for patients 12 years and older who have had flu symptoms for no more than 48 hours.

CPSC staff searched the Consumer Product Safety Risk Management System (CPSRMS) and National Electronic Injury Surveillance System (NEISS) databases, and they reviewed reports from U.S. Food and Drug Administration (FDA) related to adverse events (AEs) associated with XOFLUZA.

II. Result

Considering that XOFLUZA was approved in the United States in 2018, CPSC staff searched data from January 2015 through December 2020. Staff found no incidents related to XOFLUZA in CPSRMS[50] or NEISS[51] in this time frame.

CPSC staff also reviewed 12 reports received from FDA related to AEs associated with XOFLUZA. Of the 12 reports, five involved XOFLUZA use only; six involved multiple drug use and were considered out of scope; and one was a duplicate. Of the XOFLUZA use-only incidents, three reported no adverse effects and two reported adverse effects. Of those with adverse effects, one was not related to the drug, and one had no further information.

[50] CPSC staff searched the CPSRMS databases. These reported deaths and incidents are not a complete count of all that occurred during this period. However, they do provide a minimum number of deaths and incidents occurring during this period. Staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "XOFLUZA."

[51] NEISS injury data are gathered from emergency departments of hospitals selected as a probability sample of all U.S. hospitals with emergency departments. The surveillance data gathered from the sample hospitals enable the CPSC staff to make timely national estimates of the number of injuries associated with specific consumer products. CPSC staff searched all incidents coded under product codes 1931 (Tablet or capsule drugs), 1932 (Other drugs or medications), 1929 (Drugs or medications, not specified), and narratives mentioning "XOFLUZA."

TAB D: XOFLUZA™ (Baloxavir marboxil) Petition for Exemption from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act – Economic Considerations

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

Date: September 1, 2021

TO : Cheryl Scorpio, Ph.D.
Pharmacologist, Project Manager
Health Sciences, Pharmacology and Physiology Assessment

THROUGH: Robert Franklin
Senior Staff Coordinator
Directorate for Economic Analysis

FROM : Cynthia Gillham
Economist
Directorate for Economic Analysis

SUBJECT : XOFLUZA™ (Baloxavir marboxil) Petition for Exemption from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act – Economic Considerations

Introduction and Background

This memorandum provides information on the market for XOFLUZA™ (Baloxavir marboxil), as well as the possible economic effects of the petition.

Genentech, Inc., is a subsidiary of, and owned in its entirety by, the multinational corporation, Roche Group, headquartered in [redacted]. Roche Group employs 97,735 workers worldwide, of which 26,176 are located in North America.[52] As of February 2020, Genentech employed 13,638 people.[53]

Roche Group's operating businesses are organized into two divisions: Pharmaceuticals and Diagnostics. "Genentech, as the former third segment, has been integrated into Roche Pharmaceuticals."[54] Sales in the Pharmaceuticals Division were $48.1 billion in 2019.[55] While Roche Group reported solid overall results in 2020, pharmaceutical sales declined by 2 percent, due to impacts of the COVID-19 pandemic leading to reduced outpatient visits and the use of

[52] Roche 2019 Annual Report.
[53] "100 Best Companies to Work For". (March 24, 2020). Fortune.
[54] Roche 2019 Annual Report.
[55] Sales and other figures provided in the 2019 Roche Annual Report are given in Swiss Franc (CHF) units. U.S dollar figures are calculated assuming a 2019 constant exchange rate of 1 CHF: 0.991 USD. The appreciation of the Swiss Franc against almost all currencies had an adverse impact on 2020 financial results.

biosimilars[56] in the United States.[57] The petitioner did not provide net sales data of XOFLUZA (Baloxavir marboxil).

The Product and its Market

XOFLUZA is the trade name under which Genentech, Inc., markets baloxavir marboxil.[58] XOFLUZA (Baloxavir marboxil) is a "one-dose antiviral medication indicated for treatment of influenza for patients twelve years and older."[59] The product, which was previously available only in tablet form, is now available as flavored granules for mixing in water.[60] CR packaging is currently available for the tablet form of the product, in the following variations:

- 1 x 40 mg tablet per blister card in secondary packaging: NDC 50242-860-01
- 1 x 80 mg tablet per blister card in secondary packaging: NDC 50242-877-01

Tablets are white to light yellow in color, oblong-shaped, and film coated. XOFLUZA for oral suspension is a strawberry-flavored constituted product that may be appetizing to children. Genentech, Inc., is only requesting an exemption to CR packaging for the tablet form of the product, not the oral suspension.

In the United States, the manufacturing of plastic blister packaging falls under the North American Industry Classification System (NAICS) Sector 32619. According to the 2018 Annual Survey of Manufacturers, in the United States, approximately 397,700 workers are employed in the sector.[61]

According to Exhibit 1 of the petition made by Genentech, XOFLUZA is provided on a blister card within secondary packaging that is CR compliant. While not all types of blister packaging are CR compliant, there are a variety of ways to make blister packaging CR compliant. CR packaging is designed or constructed to be significantly difficult for children under 5 years of age to open within a reasonable time, and not difficult for normal adults to use properly.

Risks Associated with Ingestion and Patient Compliance

XOFLUZA is not approved for use in children under 12 years old.[62,63] If ingested by a child, a single dose of XOFLUZA might be considered an overdose, based on bodyweight. Treatment of an overdosage of XOFLUZA would consist of general supportive measures, including

[56] A biosimilar is a medical product that is highly similar to another biological medicine that is already approved. Biosimilars can be manufactured when the patent for the original innovator's product expires.
[57] Roche 2020 Annual Report.
[58] Covington & Burling, LLP (March 30, 2020). "Petition for Exemption for Special Packaging Requirement." Letter to the Office of the Secretary, U.S. Consumer Product Safety Commission.
[59] Covington & Burling, LLP (March 30, 2020). "Petition for Exemption for Special Packaging Requirement." Letter to the Office of the Secretary, U.S. Consumer Product Safety Commission.
[60] U.S. FDA (November 23, 2020).
[61] U.S. Census Bureau, 2018 Annual Survey of Manufacturers.
[62] Petitioner's Exhibit 1 – Prescribing Information.
[63] U.S. FDA (November 23, 2020).

monitoring of vital signs and observing the clinical status of the patient.[64] There is no specific antidote for overdose with XOFLUZA. According to information provided by the petitioner, in the case of an overdosage, "baloxavir is unlikely to be significantly removed by dialysis due to high serum protein binding." Patient information for the drug indicates XOFLUZA may cause serious side effects, including allergic reactions. It is not known if XOFLUZA is safe and effective in children under 12 years old.[65,66]

Research indicates that CR packaging reduces fatal and nonfatal child poisonings to children from unintentional ingestion of oral prescription drugs.[67] CR packaging is intended to be difficult for children to open, but still being relatively easy for adults to use. To help patients that find CR packaging difficult to use, the PPPA allows for regulated prescription drugs to be dispensed in non-child-resistant packaging, upon request of the prescribing doctor or the patient. Accordingly, staff finds approving the request for exemption from the PPPA would not significantly improve patient compliance in the prescribed treatment in the case of XOFLUZA (Baloxavir marboxil), which involves only a single-dose regimen.

Since its introduction in the 1970s, the global market for CR packaging has developed to such an extent that it is now accepted in the UK, EU, USA, Canada, and Australia, and it is rapidly gaining acceptance in China, Southeast Asia, and India.[68] Unfortunately, European testing criteria and American standards for CR packaging are not uniform, following criteria established in EN ISO 14375/BS 8404 and US 16 CFR section 17200.20, respectively.

Pharmaceutical packaging experts have found that blister packaging, like the kind currently used for XOFLUZA (Baloxavir marboxil), has many advantages.[69] Blister packaging can allow for prescriptions to be filled faster at pharmacies. Other benefits of blister packaging include better protection of the medication from moisture, oxygen, or chemical migration, which helps ensure optimal quality of tablets to the patient. Advocates of blister packaging in the United States cite product integrity, product protection, tamper evidence, reduced accidental misuse, and increased patient compliance, as advantages of blister packaging.[70] Furthermore, blister packaging is cost effective, and may be cheaper for medications dispensed in small unit doses, such as XOFLUZA, than a bottle alternative.[71]

The petitioner likely uses blister packaging for XOFLUZA for a variety of reasons, including, but not limited to, child resistance. For example, the proper storage of a XOFLUZA tablet is "in the blister package that it comes in," according to prescribing information.

Justification for the Exemption

[64] Petitioner's Exhibit 1 – Prescribing Information.
[65] Petitioner's Exhibit 1 – Prescribing Information.
[66] U.S. FDA (November 23, 2020).
[67] Rodgers, 1996.
[68] Wilkins, S. European Pharmaceutical Review. February 26, 2019.
[69] Keystone Folding Box Co., January 22, 2021.
[70] Pilchik, November 2020.
[71] Pilchik, November 2020.

Genentech is currently manufacturing XOFLUZA (Baloxavir marboxil) for the U.S. market at a production facility in [redacted]. The petitioner indicates "XOFLUZA is currently packaged at a [redacted] facility in [redacted], which has the equipment necessary to manufacture packaging that meets the Commission's child resistant packaging requirements."[72] Therefore, the petitioner has effectively indicated that it is technologically feasible and practicable to package XOFLUZA (Baloxavir marboxil) in special packaging that meets U.S. requirements.

However, Genentech wants to supplement its production at a facility in [redacted] and states in its petition that "requiring special packaging for XOFLUZA may hamper Genentech's ability to respond quickly and efficiently to an increased demand for the drug."[73] According to Genentech, the facility in [redacted] lacks the capability to manufacture special packaging needed to meet *U.S.* child resistant requirements, and "[i]t is not feasible or practical to modify the [redacted] site in a way that would allow Genentech to package XOFLUZA in child-resistant packaging in the quantities that are required."[74] However, the petitioner has not provided sufficient data or evidence to support this claim.

Data needed to evaluate the petitioner's claim might include, at a minimum, the estimated costs of CR packaging and the estimated costs of non-CR packaging. The petitioner did not provide cost estimates for machinery used in automated packaging processes to be purchased, modified, or adapted for CR-packaging production.

High-quality CR packaging for pharmaceuticals is available in a variety of locations and forms for firms to scale production. Staff found four firms that provide high-quality CR blister packaging in the [redacted], and one in [redacted]. At present, staff finds it reasonable that it is both technologically feasible and practicable to provide CR packaging from materials and equipment available in the United States and abroad.

Staff cannot conclude that requiring special packaging for XOFLUZA (Baloxavir marboxil) would hamper the firm's ability to respond quickly and efficiently to an increase in demand.

Small Business Considerations

It is the intention of the petitioner to locate packaging manufacturing for XOFLUZA (Baloxavir marboxil) in [redacted]. Such a decision could potentially result in some negative impacts for the [redacted] facility in [redacted], which is currently used to provide CR packaging for XOFLUZA, but it is unlikely to impact a substantial number of small firms.

At this time, staff cannot confirm that the loss of business at the [redacted] facility should be considered significant, or that this facility identifies as a small business. Changing the packaging requirements for only one prescription drug should not have a significant economic impact on any firm, unless packaging for that medication was a large amount of the firm's business, and

[72] Covington & Burling, LLP, March 30, 2020.
[73] Ibid.
[74] Ibid.

that packaging business could not be easily replaced. Therefore, preliminarily, staff finds that a decision on this petition by the Commission, regardless of whether it is granted, would not have a significant impact on a substantial number of small domestic firms. Accordingly, staff requests public comment on any small business impacts that might result that have not been considered.

Environmental Considerations

The Commission's regulations at 16 CFR section 1021.5 (c) states that rules exempting products from special packaging requirements under the PPPA normally have little or no potential for affecting the human environment. There is no reason to suspect that this exemption would be any different. Exempting XOFLUZA from CR packaging requirements would not have a measurable environmental impact.

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TAB E: XOFLUZA™ (Baloxavir marboxil) Petition for Exemption from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act – Special Packaging Assessment

United States
CONSUMER PRODUCT SAFETY COMMISSION
4330 East West Highway, Bethesda MD 20814

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Michael Nelson
Director, Mechanical Engineering Division
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FROM: Mark Eilbert
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SUBJECT: XOFLUZA™ (Baloxavir marboxil) Petition for Exemption from the Child-Resistant Packaging Requirements of the Poison Prevention Packaging Act – Special Packaging Assessment

BACKGROUND

In the subject petition, Genentech, Inc., requests an exemption from the special packaging requirements for its antiviral medication XOFLUZA™. The Commission's regulations allow a firm to petition for an exemption from the special packaging requirements for several reasons, including that "special packaging is not technologically feasible, practicable, or appropriate for the substance." 16 CFR § 1702.7(b).

XOFLUZA is a Food and Drug Administration (FDA)-approved novel, one-dose antiviral medication indicated for treatment of influenza (flu) for patients twelve years and older who have had flu symptoms for no more than 48 hours. Patients take a single oral dose, the entire contents of the packaging, within 48 hours of the onset of flu symptoms. Genentech seeks exemption for their one tablet, 40 mg dose (1x40 mg) and for the one tablet, 80 mg dose (1x80 mg). The petitioner contends that XOFLUZA is not toxic[75] at these doses and that special packaging is a burden when XOFLUZA may be produced in quantities to serve in a national emergency due to an influenza epidemic.

[75] Refer to the Health Sciences memorandum for the discussion on toxicity.

The definition of "package"[76] is "the immediate container or wrapping in which any household substance is contained for consumption, use, or storage by individuals in or about the household …." "Special packaging" is defined as packaging "that is designed or constructed to be difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance within a reasonable time, and not difficult for normal adults to use properly...."[77] According to 16 CFR § 1700.15, substances, including prescription drugs, listed in 16 CFR §1700.14 must have special packaging that is tested by the methods described in 16 CFR §1700.20. The petitioner provided CPSC staff a "Certificate of Compliance" issued under section 14 of the CPSA and empty physical packaging for two XOFLUZA products: a two tablet, 2 x 40 mg version and a two tablet, 2 x 20 mg version. According to the petitioner, the "entire packaging system is child-resistant and in compliance with the CPSC's regulations 16 CFR §1700.20." The petitioner announced that the 2 x 40 mg and 2 x 20 mg products would be discontinued and replaced by 1 x 40 mg and 1 x 80 mg XOFLUZA products for which they are seeking exemption. Mockup packaging were subsequently provided that are similar to the 2 x 40 mg and 2x20mg packaging products.

XOFLUZA tablets are packaged in a PVC blister on a blister card inside a folded cardboard wallet that slides out from a cardboard carton. Figure 1 shows the sequence in which the blister holding the 1x80 mg tablet is accessed. After opening the cover flap (1-2) of the carton, the consumer presses a release spot marked "A" grips the wallet at "B" and pulls the wallet out (2-3). A releasable stop inside the carton prevents the complete release of the wallet. The wallet cover is then opened, exposing the oblong blister covering of the XOFLUZA tablet[78] (3-4). The consumer pushes on the plastic blister to force the tablet out through the aluminum foil lidding on the opposing side. The sequence is similar for the 1x40 mg packaging product. Figure 2 shows the blister cards for the 1x40 mg and 1x80 mg versions. According to the petitioner, their special packaging[79] is a Type XIII Reclosable Packaging Semi-rigid (Blister), as defined in ASTM D3475-20.[80]

[76] 16 CFR § 1700.1.
[77] ibid.
[78] Genentech provided the exemplar packaging with a placebo tablet inside.
[79] Submittals indicate manufacturer is Dosepak.
[80] ASTM D3475-20 *Standard Classification of Child-Resistant Packages.*

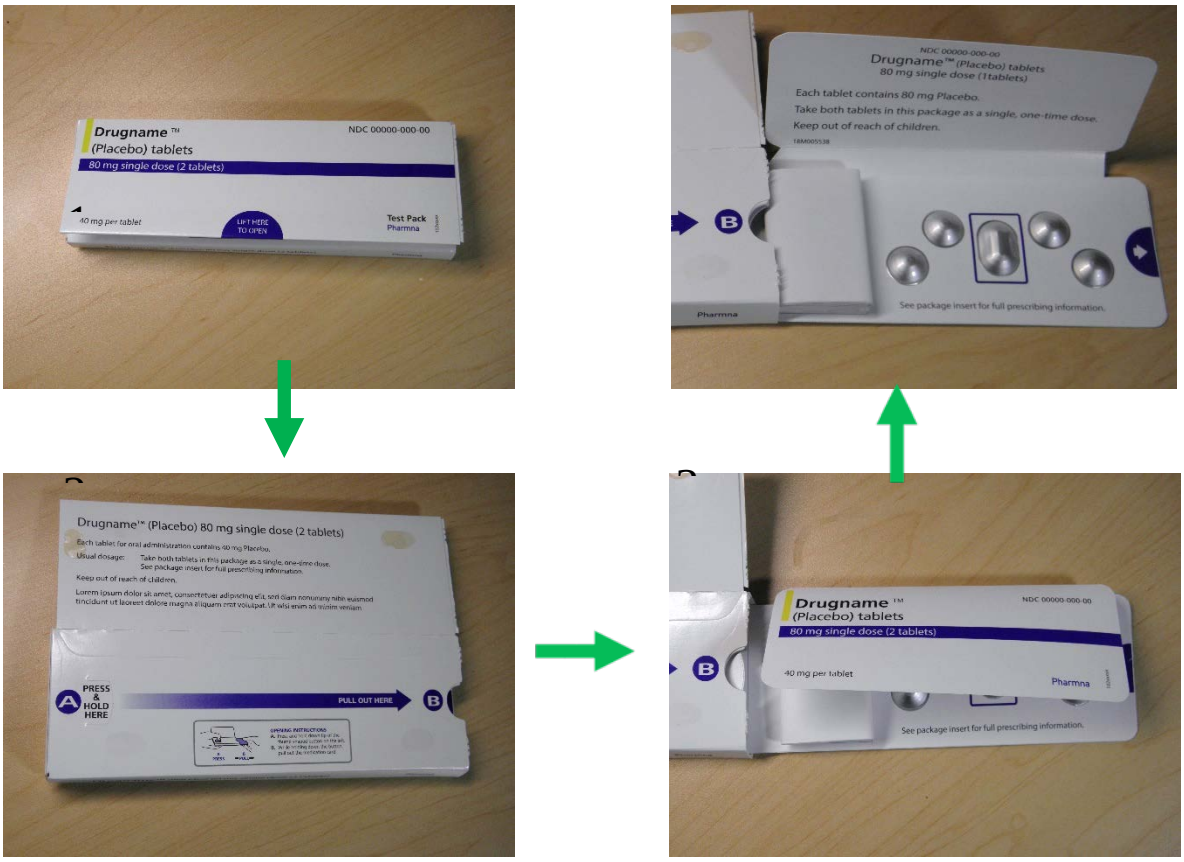

Figure 1. Packaging Mockup for XOFLUZA, One Tablet, 80 mg Dosage

Figure 2. Blister Card for XOFLUZA, 1x40 mg (left) and 1x80 mg (right)
(The tablet is placed inside the center blister in each image)

In 16 CFR §1700.14 (a), the CPSC has determined that the listed substances therein require special packaging and that the special packaging be technically feasible, practicable, and appropriate. For packaging to be considered technologically feasible, the technology must be available to produce packaging that conforms to established standards.[81] For packaging to be considered practicable, it must be adaptable to modern mass production and assembly line techniques.[82] Packaging is considered appropriate if the packaging will adequately protect the integrity of the substance it contains and will not interfere with its intended storage or use.[83] The petitioner's request for exemption must comply with 16 CFR §1702.7(b),[84] where it states that "If the exemption is requested because special packaging is not technologically feasible, practicable, or appropriate for the substance, the justification shall explain why."

[redacted] "XOFLUZA is currently packaged at a [redacted] facility in [redacted], which has the equipment necessary to manufacture packaging that meets the Commission's child-resistant packaging requirements. However, to meet the growing demand for XOFLUZA in the United States, Roche[85] intends to add an additional packaging site in [redacted]." However, [redacted] "lacks the capability to manufacture special packaging needed to meet the child resistant requirements. The material used for the child-resistant configuration requires specialized equipment that is not readily available." And, since "the process to package the tablets in child-resistant blister packs is largely manual to semi-manual, the production capacity for a child-resistant feature is ten times lower than that of a standard blister, resulting in a long lead time and limited flexibility to cope with unplanned demand."

The petitioner states that they have worked with governmental organizations that seek to stockpile drugs to combat a flu epidemic. They anticipate governments "may have similar interests in stockpiling or acquiring large volumes of XOFLUZA." However, "it is not feasible or practical to modify the [redacted] site in a way that would allow Genentech to package XOFLUZA in child-resistant packaging in the quantities that are required." Continuing, the petitioner asserted "Even if specific equipment could be installed and specific processes developed for this site, the growing demand in the United States for XOFLUZA could not be met by this site using child resistant packaging configurations." The firm does not provide an estimate for the number of doses required in a flu epidemic. Overall, the firm claims that "special packaging is not technically feasible, practicable or appropriate for XOFLUZA."

[81] S. Rep. 91-845, at 10 (1970).
[82] Ibid.
[83] Memorandum from Charles Wilbur, HSPS. to Jacqueline Ferrante. Ph.D. HSPS. "Technical Feasibility. Practicability, and Appropriateness Determination for the Proposed Rule to Require Child-Resistant Packaging for OTC Products Containing Ketoprofen." August 20. 1996.
[84] 16 CFR § 1702.7 Justification for the exemption.
[85] Roche Holding AG is the parent company of Genentech, Inc.

BASIS FOR PACKAGING EVALUTION

Staff evaluated the petitioner's claims that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA in its current special packaging and at the elevated production levels the petitioner suggests. The petitioner's justifications focus on the complexities imposed by special packaging in a planned future increase in manufacture and distribution of XOFLUZA. Staff considers that to be an argument of practicability concerning the limitations on future mass production of the petitioner's special packaging. Since the subject of 16 CFR §1702.7 (b) is the substance itself, and not a specific special packaging, staff will discuss possible alternative special packaging and its technological feasibility and how those alternatives might affect practicability.

TECHNOLOGICAL FEASIBILITY

Genentech provided exemplar special packaging and a certificate of compliance for the 2x20 mg and 2x40 mg (compliant) XOFLUZA packaging products. The petitioner has since announced the discontinuation of those compliant packages. LS staff reviewed the mockup packaging for the 1x40 mg and 1x80 mg XOFLUZA products. The salient difference between the compliant packaging and the current packaging is the shape and number of blisters. The petitioner indicated that the compliant XOFLUZA packaging is a type XIII reclosable blister, the current packaging is similar, and provided data indicating XOFLUZA has been dispensed in the U.S. and in other countries. The submittals thereby establish the technological feasibility of applying the child-resistant design of the compliant special packaging to the new XOFLUZA 1x40 mg and 1x80 mg packaging products.

The firm claimed it is not technologically feasible to modify the [redacted] site to provide special packaging for XOFLUZA. However, the compliant packaging of XOFLUZA is already feasible: technology exists to package XOFLUZA conforming to an established standard. The technical challenges to packaging are addressed later in the discussion of "practicability". Finally, other technologically feasible special packaging exists. There are more than a dozen other listed Type XIII Reclosable Packaging Semi-Rigid (Blister) designs listed in ASTM D3475-20. Additionally, a *reclosable* design is not the only option for a single tablet. Since the packaging is empty after the dose of a single tablet is accessed, an ASTM Type VIII Non-Reclosable Packaging—Semi-Rigid (Blister) design could be used for XOFLUZA special packaging. [redacted], the packaging provider for XOFLUZA, is listed in all six subcategories of the type VIII non-reclosable blister designs. Other feasible designs may also have a higher practicability than Genentech's compliant special packaging.

PRACTICABILITY

Genentech requested that they be allowed to replace their CR packaging, which may limit the overall production capacity, with a non-CR design to meet the needs of the government during a national emergency. The petitioner claims that a manual or semi-manual process limits the firm's planned expansion in production. However, blister packaging machines (blister lines) automate the complete assembly of CR packaging,[86] including those similar to Genentech's.

[86] The Uhlmann Group is one example.

Genentech alluded to a technological limit in processing speed for CR packaging. Staff finds some merit in the petitioner's claim: certain child-resistant packages do take longer to process on a blister line. Staff describes the operation of a blister line below. This information was obtained in conversations with a representative for a major packaging machine maker.
A modern blister line automates the folding, gluing, and assembly of blister packs, which includes a blister card housed within a cardboard outer package. Blister cards and their cardboard package (carton) require different work centers, due to the different materials and processes involved. They are then integrated along an assembly line on the same blister packaging machine. For example, a carton begins from a magazine holding flat carton stock, proceeds though folding and gluing operations until it receives the blister. Concurrently, the blister begins in a nearly completed state with the blisters holding the product, having been encased at a separate facility. Blister perforations and additional labelling are added, if required – *e.g.*, for a multiple-dose blister card. After insertion into the carton, the blister pack is completed with a final tuck or gluing of the flap. CR and non-CR packages can be processed on the same machine. CR packaging will require additional operations that affect the throughput of the blister line. Since adhesives require time to set, the addition of dwell times for gluing CR carton flaps constitutes a significant increase in time to process certain CR blister pack designs.

The petitioner did not describe any detail of the XOFLUZA packaging that slows its production. However, through a visual inspection of the exemplar packaging, staff believes that several glued flaps would require additional production time and that the wallet holding the blister card is an addition that requires another station on the blister line. Altogether, based on a discussion with a packaging professional, the blister line throughput of a CR packaging design with multiple cardboard assemblies is one-third to one-fifth of the rate for certain other CR carton designs. Some CR carton designs, having the same type XIII designation as XOFLUZA packaging, are assembled on a blister line at similar speeds as non-CR packages. One such design is instructive: The child-resistant feature is cut into the plastic edge of the blister card instead of formed by folding and gluing the outer carton in a blister line operation. The design also eliminates the wallet. By eliminating operations on the blister line, the production capacity can be comparable to a non-CR design. While the subject XOFLUZA packaging is adapted to mass production, and therefore, practicable, its packaging design places it at a lower production capacity on a blister line, compared to other packaging designs. The firm claims that the production capacity for a child-resistant feature is 10 times lower than for a standard blister. Staff's research indicates the Genentech packaging production capacity may be three to five times lower than other CR designs, but other suitable CR designs exist that are comparable in production capacity to non-CR designs.

Package assembly on a blister line will have an upper limit in its production capacity for each packaging design. A typical fully automated blister line can assemble up to 1,000 non-CR blister packs per minute. As discussed, CR blister pack production ranges from a small fraction of this capacity, to almost equivalency. A calculation by the packaging service provider can estimate the number of blister lines required based on a given demand. Genentech provided information on the U.S. shipments for XOFLUZA, and therefore by extension, an estimate for packaging production for a recent year. The firm did not estimate any future product demand for XOFLUZA, including demand in preparation for an epidemic. That demand would require an

outsized production response due to the size and timeliness of demand. Blister lines may be added and run on a longer schedule. Other [redacted] facilities, or other U. S. contract manufacturers, may be available to handle the elevated production levels. The firm did not discuss possible U. S. manufacturing alternatives; nor did they discuss the potential for stockpiling to address demands during an epidemic.

The petitioner projects that the future U.S. demand for XOFLUZA within special packaging cannot be met, even with the addition of the firm's intended packaging facility in [redacted]. The petitioner describes [redacted] as lacking the specialized equipment and processes to meet child resistant requirements. However, the petitioner has not explained in sufficient detail why it isn't practicable to package XOFLUZA in [redacted]. The petitioner has not provided sufficient information to claim that opening new packaging production in [redacted] is not practicable.

APPROPRIATENESS

The current packaging for XOFLUZA drug is a blister card comprising a 3-ply cold-formable aluminum-plastic laminate (blister) that is heat sealed to a push-through blister lidding. The materials in direct contact with the XOFLUZA tablets are PVC on the blister and a PVC-based heat seal coating on the lidding. Documentation provided by the firm states the "contact layer conforms to the guidelines of the FDA." Staff concludes the XOFLUZA special packaging is appropriate.

CONCLUSION

LS staff concludes that Genentech's special packaging for XOFLUZA is feasible and appropriate at all production levels and that special packaging exists that is practicable at high production levels. The firm's XOFLUZA packaging is a type listed in ASTM D3475-20 and has a certificate of compliance which meets the PPPA requirements. It is therefore technically feasible. The packaging materials in contact with XOFLUZA are approved by the FDA. The packaging is therefore appropriate. The firm's special packaging is adaptable to mass production and therefore is practicable at the current production level. Since the production capacity of the XOFLUZA special packaging is approximately three to five times lower than some other feasible special packaging designs, staff concludes those other designs are potentially more practicable at higher production levels. However, the firm did not provide information on the production capability prior to or during an epidemic or on the effects that government stockpiling may have on demand. Staff cannot conclude that XOFLUZA special packaging is not practicable at some unidentified higher production level, as the petitioner contends.

Staff concludes based on the above assessment that the petitioner has not justified that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA, and therefore, granting the petition request for an exemption on that basis is not justified under 16 CFR § 1702.17(b).

References:

Covington & Burling, LLP. Letter to the Office of the Secretary, U.S. Consumer Product Safety Commission, "Petition for Exemption from Special Packaging Requirements of the Poison Prevention Packaging Act For XOFLUZA™ (Baloxavir Marboxil)," 30 March 2020.

Covington & Burling, LLP. Letter to the Office of the Secretary, U.S. Consumer Product Safety Commission, "Amendment to Petition for Exemption from Special Packaging Requirement", 28 May 2021.

Covington & Burling, LLP. Email to Cheryl Scorpio, U.S. Consumer Product Safety Commission, "XOFLUZA Petition: Responses to Follow-Up Questions", 21 April 2021.

Covington & Burling, LLP. Email Attachment to Cheryl Scorpio, U.S. Consumer Product Safety Commission, "CPSIA Certificate of Compliance XOFLUZA", 21 April 2021.

Uhlmann Group. Telephone Conversation with Staff Engineer about Blister Lines.

16 CFR §1700 - Poison Prevention Packaging

ASTM D3475-20 Standard Classification of Child-Resistant Packages, ASTM International, 100 Barr Harbor Drive, PO Box C700, West Conshohocken, PA 19428-2959

TAB F: Draft Notice of Proposed Rulemaking

[Billing Code 6355-01-P]

CONSUMER PRODUCT SAFETY COMMISSION

16 CFR Part 1700

[Docket No. CPSC-2021-00XX]

Poison Prevention Packaging Requirements; Proposed Exemption of Baloxavir Marboxil Tablets in Packages Containing Not More that 80 mg of the Drug

AGENCY: Consumer Product Safety Commission.

ACTION: Notice of Proposed Rulemaking.

SUMMARY: The Consumer Product Safety Commission (Commission or CPSC) is proposing to amend the child-resistant packaging requirements to exempt baloxavir marboxil tablets in packages containing not more that 80 mg of the drug, currently marketed as XOFLUZA,™ from the special packaging requirements. XOFLUZA is used to treat the flu, and is taken in one dose within 48 hours of experiencing flu symptoms. The proposed rule would exempt this prescription drug product on the basis that child-resistant packaging is not needed to protect young children from serious injury or illness because the product is not acutely toxic and lacks adverse human experience associated with ingestion.

DATES: Comments should be submitted no later than [**insert date 75 days after date of publication in the FEDERAL REGISTER**].

ADDRESSES:

You may submit comments, identified by Docket No. CPSC- 2021-00XX, by any of the following methods:

Electronic Submissions: Submit electronic comments to the Federal eRulemaking Portal at: https://www.regulations.gov. Follow the instructions for submitting comments. The CPSC does not accept comments submitted by electronic mail (e-mail), except through https://www.regulations.gov. The CPSC encourages you to submit electronic comments by using the Federal eRulemaking Portal, as described above.

Mail/hand delivery/courier Written Submissions: Submit comments by mail/hand delivery/courier to: Division of the Secretariat, Consumer Product Safety Commission, 4330 East West Highway, Bethesda, MD 20814; telephone (301) 504-7479.

Instructions: All submissions received must include the agency name and docket number for this notice. All comments received may be posted without change, including any personal identifiers, contact information, or other personal information provided, to: https://www.regulations.gov. Do not submit electronically confidential business information, trade secret information, or other sensitive or protected information that you do not want to be available to the public. If you wish to submit such information please submit it according to the instructions for written submissions.

Docket: For access to the docket to read background documents or comments received, go to: https://www.regulations.gov, and insert the docket number, CPSC- 2021-00XX, into the "Search" box, and follow the prompts.

FOR FURTHER INFORMATION CONTACT:

Cheryl A. Scorpio, Ph.D., Division of Pharmacology and Physiology Assessment, Directorate for Health Sciences, Consumer Product Safety Commission, 5 Research Place, Rockville, MD 20850; telephone (301) 987-2572; cscorpio@cpsc.gov.

SUPPLEMENTARY INFORMATION:

A. Background

1. The Poison Prevention Packaging Act of 1970 and Implementing Regulations

The Poison Prevention Packaging Act of 1970 (PPPA), 15 U.S.C. 1471–1476, gives the Commission authority to establish standards for the "special packaging" of household substances, such as drugs, when child-resistant (CR) packaging is necessary to protect children from serious personal injury or illness due to the substance, and the special packaging is technically feasible, practicable, and appropriate for such substance. 15 USC § 1472(a). Special packaging requirements under the PPPA have been codified at 16 CFR parts 1700 and 1702. Specifically, CPSC regulations require special packaging for oral prescription drugs. 16 CFR § 1700.14(a)(10). CPSC regulations allow companies to petition the Commission for an exemption from CR requirements. 16 CFR Part 1702. Two "reasonable grounds"[87] for granting an exemption from the special packaging requirements are: (1) that the degree or

[87] A third reasonable ground for an exemption is that special packaging is incompatible with the particular substance. 16 CFR §1702.17(c). The petitioner has not requested an exemption on this basis so it is not relevant here.

nature of the hazard to children in the availability of the substance, by reason of its packaging, is such that special packaging is not required to protect children from serious personal injury or serious illness resulting from handling, using or ingesting the substance; or (2) special packing is not technically feasible, practicable, or appropriate for the subject substance. 16 CFR §1702.17(a) and (b).

If the Commission determines that reasonable grounds for an exemption are presented by a petition, CPSC regulations require publication in the *Federal Register* of a proposed amendment to the listing of substances that require special packaging, stating that the substance at issue is exempt. 16 CFR § 1702.17.

2. The Product for Which an Exemption Is Sought

On March 30, 2020, Genentech, Inc. (Genentech), petitioned the Commission to exempt two specified sized tablets of baloxavir marboxil, which it markets as XOFLUZA from the special packaging requirements for oral prescription drugs. XOFLUZA was approved by the U.S. Food and Drug Administration (FDA) in October 2018, with a two-tablet dose for the acute uncomplicated flu in patients older than 12 years old showing symptoms for less than 48 hours. Single tablet doses have recently been approved by the FDA in March 2021. XOFLUZA has been marketed in tablet form and is currently dispensed in CR packaging. The petitioner asserted that an exemption from special packaging is justified because of the lack of toxicity and lack of adverse human experience with the drug. The petitioner also claimed that special packaging is not technically feasible, practicable, or appropriate for XOFLUZA. Staff's briefing memorandum provides a detailed assessment of the petitioner's claims regarding a

request for an exemption from the special packing requirements for XOFLUZA. [INSERT WEBLINK HERE]

B. Toxicity and Injury Data for XOFLUZA

Toxicity

CPSC staff reviewed the toxicity of XOFLUZA. XOFLUZA has been studied in pediatric patients (Hirotsu, 2019; Heo, 2018; NCT03653364, CAPSTONE 2; Hayden, 2018; Dziewiatkowski et al., 2019). Overall, clinically relevant doses of XOFLUZA (40 or 80 mg total dose) in humans are well tolerated (Dziewiatkowski et al., 2019; Taieb et al., 2019; Ng, 2019; Hayden, 2018).

The analysis of total adverse events (AE) included 10 studies with six treatments and 5628 patients. AE did not differ significantly between placebo and XOFLUZA. For drug-related vomiting, 3297 patients from five studies were included. XOFLUZA did not differ from placebo in these studies. (Taieb et al., 2019). The percentage of patients experiencing any adverse event[88] of 610 patients (12 to 64 years old) in the CAPSTONE 1 clinical trial was 1.0% grade 3 or grade 4, which can be categorized as not serious. Five deaths have been reported by the AER System[89]; however, these deaths have been determined to not be related to XOFLUZA.

The most common AE of the correct dose of XOFLUZA was diarrhea (Heo, 2018; Shionogi prescribing info). The XOFLUZA Product Information, 2021 reported

[88] The adverse events are: diarrhea, bronchitis, nasopharyngitis, nausea, sinusitis, increase in the level of AST, headache, vomiting, dizziness, leukopenia and constipation.

[89] The **Adverse Event Reporting System** (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to monitor for new adverse events and medication errors that might occur with these marketed products.

that diarrhea (3%), bronchitis (3%), nausea (2%), headache (1%) were the most significant adverse events found.

Treatment of an overdose of XOFLUZA should consist of general supportive measures, including monitoring of vital signs and observations of the clinical status of the patient. There is no specific antidote for overdose with XOFLUZA and it is unlikely to be significantly removed by dialysis because it is highly protein bound (Prescribing Information for XOFLUZA, 2021; Poisindex, 2021).

Overall, treatment with XOFLUZA is well tolerated. If accidentally ingested, the greatest potential for injury is diarrhea, nausea, and headache. For these reasons, CPSC staff determined that XOFLUZA will not cause serious injury or death upon acute exposure by a child under 5 years old.

Injury Data

CPSC staff searched the Consumer Product Safety Risk Management System (CPSRMS), the National Electronic Injury Surveillance System (NEISS) databases, and reviewed reports from FDA related to adverse events associated with XOFLUZA. CPSC staff found no incidents related to XOFLUZA in CPSRMS or NEISS from January 2015 through December 2020. CPSC staff also reviewed 12 reports received from FDA related to adverse events associated with XOFLUZA. Of the 12 reports, five involved XOFLUZA use only. Of these five incidents, two reported adverse effects. One patient experienced hallucination, fever, and sore throat, and the other patient suffered cardiac failure. Both were unrelated to XOFLUZA. Six incidents involved use of multiple drugs and were considered out of scope, and one was a duplicate.

C. Action on the Petition

After considering the information provided by the petitioner and other available toxicity and human experience data, the Commission concluded preliminarily that the "lack of toxicity and lack of adverse human experience for the substance" presented by the availability of 40 mg and 80 mg tablets of baloxavir marboxil (currently marketed as XOFLUZA) is such that special packaging is not required to protect children from serious injury or serious illness from handling, using, or ingesting XOFLUZA. 16 CFR § 1702.17(a). Additionally, the Commission found that the petitioner's request for an exemption from special packaging, on the basis that it is not technically feasible, practicable, or appropriate for XOFLUZA, was not warranted based upon the information provided by the petitioner. Therefore, the Commission determined that reasonable grounds for an exemption were presented based on toxicity and voted to grant the petition and begin a rulemaking proceeding to exempt baloxavir marboxil tablets in packages containing not more that 80 mg of the drug from the special packaging requirements for oral prescription drugs.

Once the Commission determines that reasonable grounds for an exemption are presented by the petition, CPSC regulations require publication in the *Federal Register* of a proposed amendment to the listing of substances that require special packaging, stating that the substance at issue is exempt. 16 CFR § 1702.17. This document proposes to amend the listing of substances in 16 CFR part 1700 that require special packing to state that baloxavir marboxil tablets in packages containing not more that 80 mg of the drug do not require special packing.

D. Description of the Proposed Rule

The proposed rule would amend 16 CFR part 1700 to include a new exemption from the special packaging requirements for baloxavir marboxil tablets in packages containing not more that 80 mg of the drug in proposed § 1700.14(a)(10)(xxiv). The proposed exemption is intended to cover baloxavir marboxil tablets for any dosage from 80 mg or below. The proposed rule would make no other changes to part 1700.

E. Regulatory Flexibility Act

Under the Regulatory Flexibility Act (RFA; 5 U.S.C. 601 et seq.), an agency that engages in rulemaking generally must prepare initial and final regulatory flexibility analyses describing the impact of the rule on small businesses and other small entities. Section 605 of the Act provides that an agency is not required to prepare a regulatory flexibility analysis if the head of an agency certifies that the rule will not have a significant economic impact on a substantial number of small entities.

CPSC staff prepared a preliminary assessment of the impact of the proposed rule to exempt baloxavir marboxil in 40 mg and 80 mg tablet form, currently marketed as XOFLUZA, from special packaging requirements. Genentech, Inc., is a subsidiary of, and owned in its entirety by the multinational corporation, Roche Group, the company that markets XOFLUZA. Roche Group employs 97,735 workers worldwide, of which 26,176 are located in North America. As of February 2020, Genentech employed 13,638 people. Roche Group's operating businesses are organized into two divisions: Pharmaceuticals and Diagnostics. Genentech, as the former third segment, has been integrated into

Roche Pharmaceuticals. Sales in the Pharmaceuticals Division were $48.1 billion in 2019.

There are two main economic reasons for why granting the petition would not result in the exemption having a significant economic impact on a substantial number of small entities. First, the exemption for this drug is not likely to impact a large number of firms, therefore it is unlikely that granting the petition would impact a substantial number of small entities. Second, CR packaging for XOFLUZA tablets is unlikely to be a significant amount of any firm's business, therefore granting the petition would not have a significant economic impact on any small entity. However, if the petitioner relocates packaging to another country, it could potentially result in some minor negative impacts for small domestic firms. Based on this assessment, we preliminarily conclude that the proposed amendment exempting baloxavir marboxil tablets in packages containing not more that 80 mg of the drug would not have a significant impact on a substantial number of small businesses or other small entities. We seek public comment on any small business impacts that might result from the exemption in the proposed rule.

F. Effective Date

The Administrative Procedure Act (APA) generally requires that a substantive rule must be published not less than 30 days before its effective date. 5 U.S.C. 553(d)(1). The NPR proposes an effective date of 30 days after publication of the final rule in the *Federal Register,* because the proposed rule would provide an exemption from the requirement to use special packaging for baloxavir marboxil tablets in packages containing not more that 80 mg of the drug.

G. Environmental Considerations

The Commission's regulations provide a categorical exclusion for the Commission's rules from any requirement to prepare an environmental assessment or an environmental impact statement where they "have little or no potential for affecting the human environment." 16 CFR 1021.5(c)(3). Rules exempting products from poison prevention packaging rules fall within the categorical exclusion, so no environmental assessment or environmental impact statement is required.

H. Preemption

The PPPA provides that, generally, when a special packaging standard issued under the PPPA is in effect, "no State or political subdivision thereof shall have any authority either to establish or continue in effect, with respect to such household substance, any standard for special packaging (and any exemption therefrom and requirement related thereto) which is not identical to the [PPPA] standard." 15 U.S.C. 1476(a). A state or local standard may be excepted from this preemptive effect if: (1) the state or local standard provides a higher degree of protection from the risk of injury or illness than the PPPA standard; and (2) the state or political subdivision applies to the Commission for an exemption from the PPPA's preemption clause and the Commission grants the exemption through a process specified at 16 CFR part 1061. 15 U.S.C. 1476(c)(1). In addition, the federal government, or a state or local government, may establish and continue in effect a nonidentical special packaging requirement that provides a higher degree of

protection than the PPPA requirement for a household substance for the federal, state, or local government's own use. 15 U.S.C. 1476(b).

Thus, with the exceptions noted above, the proposed rule exempting baloxavir marboxil tablets in packages containing not more that 80 mg of the drug from special packaging requirements, if finalized, would preempt nonidentical state or local special packaging standards for the substance.

List of Subjects in 16 CFR Part 1700

Consumer protection, Drugs, Infants and children, Packaging and containers, Poison prevention, Toxic substances.

For the reasons given above, the Commission proposes to amend 16 CFR part 1700 as follows:

PART 1700--[AMENDED]

III. The authority citation for part 1700 continues to read as follows:

Authority: 15 U.S.C. 1471–76. Secs. 1700.1 and 1700.14 also issued under 15 U.S.C. 2079(a).

IV. Section 1700.14 is amended by revising to add a new paragraph (a)(10)(xxiv) to read as follows:

Sec. 1700.14 - Substances requiring special packaging.

(a) * * *

(10) * * *

(xxiv) Baloxavir marboxil tablets in packages containing not more that 80 mg of the drug.

* * * * *

Dated: _____

_____

Alberta E. Mills, Secretary
U.S. Consumer Product Safety Commission