CITIZEN PETITION

Requesting Approval and Issuance of Draft Guidance Document Supporting the Routine Testing of Drugs and Biologic Materials for Ototoxicity Potential

To:

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Norman E. Sharpless, M.D.
Acting Commissioner of Food and Drugs
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

GUIDANCE DOCUMENT SUBMISSION

Dear Dr. Sharpless,

The undersigned submit this petition under Section 701(h) of the Federal Food, Drug, and Cosmetic Act and under Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.115(f)(3) to request the Commissioner of Food and Drugs to approve and issue the attached draft guidance document, "Ototoxicity: Nonclinical Evaluation During Drug Development". We believe that current regulatory requirements do not lead to adequate detection and prevention of harm to hearing and balance caused by medication use, and that the potential for clinically significant damage to hearing and balance is underappreciated.

A. Action Required

FDA should approve and issue the attached draft guidance document, "Ototoxicity: Nonclinical Evaluation During Drug Development".

B. Statement of Grounds

1. Summary of Auditory Anatomy, Physiology, and Dysfunction

Adequately appreciating the impact of ototoxicity requires a basic understanding of how the ears work, and what causes them to be impaired. This section will present a brief summary of the anatomy of the ears, their proper functioning, and the ways that hearing and balance can become dysfunctional.

The human ear, like that of other mammalian species, is generally divided into three anatomic regions: outer, middle, and inner.

- The outer ear is composed of the large and folded auricle, the ear canal, and the tympanic membrane (eardrum).
- The middle ear is a space of approximately 3-5 ml in volume, and is air-filled in the absence of disease. The primary middle ear structures are three bones connected in series: the malleus, incus, and stapes. The malleus is connected to the inside of the tympanic membrane; the incus is connected to the malleus; and the stapes bridges the distance from the incus to a hole in the skull called the oval window.
- The inner ear is contained in dense bone and includes special sense organs of hearing (the cochlea) and balance (the utricle, saccule, and semicircular canals). Nerves come from each of these special sense organs, and collectively are referred to as the auditory (hearing) nerve and the vestibular (balance) nerve. These nerves mainly carry signals from the ears to the brain, but also carry some modifying signals from the brain to the ears.

The overall function of the outer and middle ears is to convert sound energy to mechanical energy. The outer ear focuses and delivers sound waves traveling through air to the tympanic membrane, and provides subtle amplification of sound wave energy. The tympanic membrane vibrates with this sound energy, thus converting it to mechanical energy. This mechanical energy is transmitted via the bones of the middle ear, as each bone pushes on the next. The area of the tympanic membrane is approximately 14 times greater than the end surface of the stapes, which greatly increases the effectiveness of energy transfer as it is directed to the oval window.

Thus, proper functioning of the outer and middle ears depends on physical (mechanical) changes – each structure is basically pushing the next, causing vibrations to be transmitted along a series of structures. The inner ear, in contrast, converts these mechanical forces into electrical energy. Vibration of the stapes pushes fluid in the cochlea, which causes microscopic filaments on specialized cells, called hair cells, to bend. As the hairs bend, the electric potential of each hair cell changes. These electrical changes generate nerve impulses that are carried to the brain. The balance organs (the utricle, saccule, and semicircular canals) function in a similar manner: changes in head position cause fluid to shift and hairs to bend, generating nerve impulses and giving a sense of movement or alteration in position.

As the function of the outer and middle ears (mechanical energy transduction) differs from that of the inner ear (electrical energy transduction), so do the general causes of dysfunction. Problems in the outer and middle ears are generally caused by macroscopic physical changes that prevent proper movement of structures. For example, a hole in the tympanic membrane might prevent it from vibrating, or fluid in the middle ear space can limit the ability of the three bones to move. Hearing loss from these conditions is called "conductive" hearing loss, as it relates to physical inability to conduct energy.

Inner ear dysfunction, by contrast, often involves damage to microscopic structures like the hair cells, or physiologic problems such as the inability of cells to maintain proper electrical potential and thus lose the power to generate nerve impulses. When hearing loss results from these conditions, it is referred to as "sensorineural" hearing loss. Balance issues resulting from inner ear pathology are collectively referred to as vestibular dysfunction.

Loss of hearing is not the only potential consequence of inner ear damage. Tinnitus, commonly thought of as ringing in the ears or head, is defined as the conscious perception of sound when no corresponding external sound source is present. Theories about the pathophysiology of tinnitus, and the sites in the ears and brain where it may be generated, are varied. In some cases, tinnitus is caused by cellular, electrical, and/or neural dysfunction in the cochlea. In other cases, tinnitus may be generated within the brain when auditory neural pathways attempt to boost the diminished input from damaged cochleae and create the perception of sound in the process. In almost all cases, though, reduced input from the cochlea is the predisposing condition, leading to hyperactivity in the brain's hearing circuits. This is supported by evidence that restoring cochlear output to the brain, through cochlear implants or hearing aids, can reduce the perception of tinnitus[1].

2. Current Treatments for Auditory Dysfunction

Because conductive hearing loss is generally caused by physical alterations to relatively large structures, a variety of treatment options exists to reverse most pathologic changes. Many surgical procedures are available to correct conductive problems, such as patching holes in the tympanic membrane, widening a narrow ear canal, replacing a defective middle ear bone, or releasing the stapes which can be stuck due to bony overgrowth. Several medicinal treatments exist to treat conductive hearing loss due to infections, fluid in the middle ear, or excessive negative pressure in the middle ear space.

Sensorineural hearing loss, by contrast, is considered to be irreversible in almost all cases. Because sensorineural pathology is generally microscopic or physiologic in nature, surgical treatments are not available to restore inner ear function. Cochlear implantation can be considered in patients with profound hearing loss or deafness, but this surgical approach effectively removes the remaining sensory structures of the cochlea entirely, and provides the patient with a welcome but altogether different sense of sound perception. Non-surgical options are also very limited, as most forms of sensorineural hearing loss are rooted in loss of hair cells or the loss of connection between hair cells and the auditory nerve. These cells are very fragile and do not regenerate, so medicines are unable to reverse this permanent loss of hair cells. The only accepted non-surgical treatment for patients with sensorineural hearing loss is the use of hearing aids. While helpful for many patients, hearing aids are not beneficial to everyone, and do not truly restore original function but rather help patients to cope with their loss of auditory ability by amplifying sounds to intensity levels they can hear.

3. Why Hearing Matters

It is difficult to truly appreciate the effects of hearing loss until a person experiences it. Unlike the eyes, which can simply be closed, there is no way to "turn off" the ears. It is possible, therefore, that people without hearing loss may take for granted the contributions of hearing to daily life. Hearing contributes to awareness and safety because, unlike sight, it is multi-directional and can locate the distance and direction of a threatening event, providing warnings even during sleep. Hearing is essential for satisfactory communication, as a typical person speaks

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[1] Haider, H.F., Bojic, T., Ribeiro, S.F., Paco, J., Hall, D, & Szczepek, J. (2018). Pathophysiology of subjective tinnitus: triggers and maintenance. Front Neurosci, 12:866.

thousands of words per day and hearing these words allow for understanding of ideas and emotional cues from the speaker. Hearing is also crucial for the enjoyment of life, through participating in activities that depend on sound such as listening to music and other media, or simply appreciating the richness of one's surroundings.

4. Consequences of Mild to Moderate Hearing Loss

It may be tempting to conclude that patients with hearing loss do not suffer significant consequences of this condition unless the loss is profound, at which point hearing aids or cochlear implantation may not be effective or justified. However, significant evidence exists that mild or moderate sensorineural hearing loss, even when compensated by hearing aids or cochlear implants, can lead to multiple negative sequelae for both adults and children.

Consequences of Mild to Moderate Hearing loss in Adults

In medical and scientific literature, there is often an assumption that the psychosocial consequences of hearing loss on adults, such as communication difficulties, social isolation, cognitive impairment, lower wages, and depression, apply mostly to elderly adults, usually with more severe forms of hearing loss[2]. In reality, adults with mild and moderate hearing loss report primarily negative consequences of this handicap, including poor identity (feeling old and unintelligent), decreased participation in social activities, communication and relationship difficulties, fewer community and professional activities, and more loneliness[3].

Hearing loss in adults is known to be an independently associated risk factor for poor cognitive function and early onset of dementia[4], and this association is true when specifically considering adults with mild and moderate hearing loss. Cognitive testing scores (including assessment of orientation, concentration, language, praxis, memory, and executive function) have been shown to decline 30-40% faster in individuals with hearing loss beginning with only a 25 dB threshold shift (defined as mild hearing loss), and increase in direct proportion with the severity of an individual's baseline hearing loss[5].

Dementia (memory loss) is also more prevalent among adults with mild or moderate hearing impairment. The increased risk of dementia becomes evident for hearing loss of only 25 dB, and increases in a significant log-linear relationship with each small, incremental hearing threshold shift beyond this[6]. In this same study, the rate of dementia incidence was almost twice as high for

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[2] Monzani, D., Galeazzi, G.M., Genovese, E., Marrara, A., & Martini, A. (2008). Psychological profile and social behaviour of working adults with mild or moderate hearing loss. Acta Otorhinolaryngologica Italica 28, 61-66.

[3] Heffernan E., Coulson, N.S., Henshaw, H., Barry, J.G., & Ferguson, M.A. (2016). Understanding the psychosocial experiences of adults with mild-moderate hearing loss: an application of Leventhals's self-regulatory model. Int J Audiol 55(Suppl 3), S3-S12.

[4] Fortunato, S., Forli, F., Guglielmi, V., de Corso, E., Paludetti, G., Berrettini, S., & Fetoni, A.R. (2016). A review of new insights on the association between hearing loss and cognitive decline in ageing. Acta Otorhinolaryngologica Italica 36, 155-166.

[5] Lin, F.R., Yaffe, K., Xia, J., Xue, Q-L., Harris, T.B., Purchase-Helzner, E., et al. (2013). Hearing loss and cognitive decline among older adults. JAMA Intern Med 173(4), 1-14.

[6] Lin, F.R., Metter, E.J., O'Brien, R.J., Resnick, S.M., Zonderman, A.B., & Ferrucci, L. (2011). Hearing loss and incident dementia. Arch Neurol 68(2), 214-220.

patients with mild hearing loss and three times as high for patients with moderate hearing loss compared to normal hearing individuals.

Hearing impairment can understandably lead to frustration and decreased participation in social and professional activities, but these restrictions are not limited to older or more severely hearing-impaired individuals. Among a cohort of men and women with a mean age of 46 years and mild or moderate hearing loss, participation in social activities was significantly reduced, relational problems with family and friends were increased, and emotional difficulties at work were higher than matched controls with no hearing loss[2.] Younger individuals with hearing loss are also more likely to seek early retirement. Two separate cross-sectional studies showed that working men age 31-45 years were approximately 1.5x more likely to seek early retirement for each small (10 decibel) hearing loss compared to normal hearing workers[7].

Mild to moderate hearing loss has been demonstrated to reduce quality of life and increase rates of depression in adults. Among a cohort of 472 individuals of whom 106 had mild to moderate hearing loss, quality of life (defined by emotional, social, and communication function) was significantly reduced in those with hearing loss, and this handicap was perceived as "severe" by those affected[8]. A separate cross-sectional study of 1,328 participants age 60 years and above found that mild hearing loss was associated with a significantly (1.83x) higher risk of depressive symptoms compared to normal hearing individuals[9]. Among younger, working individuals, mild and moderate hearing impairment was associated with significantly worse psychological well-being than normal hearing subjects, especially if their professions involved high-stress work[2].

Consequences of Mild to Moderate Hearing loss in Children

There is significant evidence in pediatric hearing literature that even mild hearing loss or delayed hearing leads to high costs for children in terms of overall health, psychological well-being, and social integration[10].

One area in which children with mild or moderate hearing loss suffer is education[11]. A large, education-based study showed that children with mild hearing loss (approximately 5% of 1,200 students surveyed) exhibited significantly lower test scores on comprehensive basic skills tests in third grade, and 37% of surveyed students with mild hearing loss had failed at least one grade[12]. In another study of older children who survived cancer treatment but experienced hearing loss

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[7] Helvik, A-S., Krokstad, S., & Tambs, K. (2012). Hearing loss and risk of early retirement. The HUNT study. Eur J Pub Health 23(4), 617-622.

[8] Mulrow, C.D., Aguilar, C., Endicott, J.E., Velez, R., Tuley, M.R., Charlip, W.S., & Hill, J.A. (1990). Association between hearing impairment and the quality of life of elderly individuals. J Am Geriatr Soc 38(1), 45-50.

[9] Gopinath, B., Wang, J.J., Schneider, J., Burlutsky, G., Snowdon, J., McMahon, C.M., Leeder, S., & Mitchell, P. (2009). Depressive symptoms in older adults with hearing impairment: the Blue Mountains Study. J Am Gereatr Soc 57(7), 1306-1308.

[10] Bass, J.K., Knight, K.R., Yock, Y.I., Chang, K.W., Cipkala, D., & Grewal, S.S. (2016). Evaluation and management of hearing loss in survivors of childhood and adolescent cancers: a report from the Children's Oncology Group. Pediatr Blood Cancer 63(7), 1152-1162.

[11] Hornsby, B.W.Y., Gustafson, S.J., Lancaster, H., Cho, S-J., Camarata, S., & Bess, F.H. (2017). Subjective fatigue in children with hearing loss assessed using self- and parent-proxy report. Am J Audiol 26, 393-407.

[12] Bess, F.H., Dodd-Murphy, J., & Parker, R.A. (1998). Children with minimal sensorineural hearing loss: prevalence, educational performance, and functional status. Ear Hear 19(5), 339-354.

related to treatment, the risk of learning difficulty in reading, math, and general studies was at least twice as high as normal hearing cancer survivors[13].

Mild to moderate hearing loss can also lead to increased fatigue and stress for students. In a study of 60 students with mild or moderate hearing loss, self-reported classroom fatigue was significantly higher compared to normal hearing students[11]. This was presumably due to the increased attention and concentration needed for listening in the classroom. Increased classroom fatigue is also related to higher levels of stress experienced by students with hearing loss, again likely due to the higher demands on students to listen during school[14].

Outside of the classroom, children with mild or moderate hearing loss suffer from a variety of psychosocial problems. Such children display lower observed and self-reported quality of life scores[13], and significantly greater dysfunction than children with normal hearing in terms of behavior, energy, stress, social support, and self-esteem[12].

Children with mild or moderate hearing loss are therefore at a disadvantage in terms of educational performance and psychosocial well-being, and even as adults the consequences can be significant. Children with hearing loss are up to 39% less likely to attend college, are twice as likely to experience work stress, and have lower labor participation rates than normal hearing individuals[15].

5. Ototoxicity

Ototoxicity is the cellular degeneration of the cochlea or vestibular tissues, resulting from the exposure to certain therapeutic agents or chemicals, that leads to functional deterioration[16]. One of the most common symptoms of ototoxicity is hearing loss, which is sensorineural in nature because cellular damage occurs in the cochlea. Other signs and symptoms of ototoxicity are tinnitus, hyperacusis (discomfort resulting from perception of loud sounds), pressure or fullness in the ears, dizziness, and vertigo.

Certain classes of medications are known to be especially likely to cause significant ototoxic damage. These include:

- Platinum-based chemotherapeutic agents: Medications such as cisplatin, carboplatin, oxaliplatin, and other platinum-based chemotherapeutic drugs are widely used in adults against solid tumors of the head and neck, lung, ovary, testicle, and bladder, and in children against neuroblastomas, osteosarcomas, hepatoblatomas, germ cell tumors, and central nervous system tumors. The overall prevalence of ototoxicity ranges widely, but

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[13] Gurney, J.G., Tersak, J.M., Ness, K.K., Landier, W., Matthay, K.K., Schmidt, M.L., & Children's Oncology Group. (2007). Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group. Pediatrics 120(5), 1229-1236.
[14] Bess, F.H., Gustafson, S.J., Corbett, B.A., Lambert, E.W., Camarata, S.M., & Horsnby, B.W. (2016). Salivary cortisol profiles of children with hearing loss. Ear Hear 37(3), 334-344.
[15] Roland, L., Fischer, C., Tran, K., Rachakonda, T., Kallogjeri, D., & Lieu, J. (2016). Quality of life in children with hearing impairment: systematic review and meta-analysis. Otolaryngol Head Neck Surg 155(2), 208-219.
[16] Ganesan, P., Schmiedge, J., Manchaiah, V., Swapna, S., Dhandayutham, S., & Kothandaraman, P.P. (2018). Ototoxicity: a challenge in diagnosis and treatment. J Audiol Otol 22(2), 59-68.

reaches 90% in high-risk groups and can lead to severe hearing loss in up to 71% of patients[17].

- Certain anti-infective medications such as aminoglycosides, macrolides, vancomycin, and anti-malarial treatments: Aminoglycosides (gentamicin, streptomycin, neomycin, kanamycin, tobramycin, and amikacin) are possibly the best-known antibiotics to cause ototoxic hearing loss and vestibular dysfunction, which occur in approximately 20% of patients who receive these drugs intravenously for multiple days[18].
- Loop diuretics: Widely used in edematous states, congestive heart failure, and hypertension, loop diuretics such as furosemide are known to cause moderate ototoxic hearing loss that is usually temporary. However, if used in combination with other ototoxic medications, as if often indicated in treatment of malignancies and infections, hearing loss can be more severe and permanent[19].
- Erectile dysfunction drugs: Phosphodiesterase type 5 (PDE-5) inhibitors are a class of drugs used to treat erectile dysfunction and pulmonary artery hypertension. The first case of profound, permanent bilateral deafness after taking one PDE-5 inhibitor, sildenafil (Viagra), was published nine years after FDA approval of this medication[20]. After realizing that dozens of other reports of hearing loss after PDE-5 use existed, the FDA began requiring that hearing loss be listed as a potential side effect of these drugs[21]

More generally, ototoxic side effects are very common among all medications. The SIDER Side Effect Resource version 4.1 accumulates side effect data from publicly available resources, including medication labels, of 1,430 currently marketed medications. SIDER reports that 395 (27.6%) of these approved medications have the potential to cause tinnitus, 122 (8.5%) have the potential to cause hearing impairment, and 110 (7.7%) have the potential to cause deafness. Vertigo and other vestibular disorders are linked to 508 (35.5%) of medications[22].

6. Current regulatory environment

Despite the high prevalence of ototoxic side effects among presently approved drugs, there is currently no requirement that new medications be screened for ototoxic potential. In 2003, at the request of the FDA, the Society of Toxicologic Pathology (STP) created a recommended list of 42 core tissues to be tested histopathologically in repeat-dose toxicity and carcinogenicity

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[17] Landier, W., Knight, K., Wong, F.L., Lee, J., Thomas, O., Kim H., et al. (2014). Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales – a report from the Children's Oncology Group. J Clin Oncol 32(6), 527-539.
[18] Jiang, M., Karasawa, T., & Steyger, P.S. (2017). Aminoglycoside-induced cochleotoxicity: a review. Front Cell Neurosci 11:308.
[19] Ding, D., Liu, H., Qi, W., Jiang, H., Li, Y., Wu, X., Sun, H., Gross, K., & Salvi, R. (2016). Ototoxic effects and mechanisms of loop diuretics. J Otol 11, 145-156.
[20] Mukherjee, B., & Shivakumar, T. (2007). A case of sensorineural deafness following ingestion of sildenafil. J Laryngol Otol, 121, 395-397.
[21] McGwin, G. (2010). Phosphodiesterase type 5 inhibitor use and hearing impairment. Otolaryngol Head Neck Surg, 136(5), 488-492.
[22] SIDER 4.1 (2015), Side Effect Resource. http://sideeffects.embl.de, (June 13, 2019).

studies[23]. However, the ears were the only major organ or sensory system not included in this list.

The FDA has commented in the recent past on the importance of ototoxicity screening. In a guidance document issued in 2015, it was recommended that "If [a] drug product is expected to reach the middle or inner ear during clinical use or is introduced directly to those regions, evaluation of the auditory brainstem response, as well as microscopy of relevant otic tissue, including a cytocochleogram, should be included in acute and/or repeat-dose studies conducted by intratympanic administration"[24]. However, this guidance document was specific only to reformulated drug products and products for which a new route of administration was being evaluated. Therefore, its influence on the ototoxic screening of new drug products was likely minimal.

7. Importance of Ototoxicity Testing

Few members of the regulatory, pharmacology, and biotechnology communities would deny that hearing is important. However, when considering the necessity for ototoxicity screening and prevention, many drug developers and regulatory experts assume that only severe consequences of ototoxicity (profound hearing loss and deafness) are worthy of preventative efforts. It is often concluded that if a drug causes mild-to-moderate hearing loss, this is a small and acceptable price to pay for the drug's therapeutic benefits. Additionally, it is likely that only profound consequences of ototoxicity are ever noticed, as was the case with deafness following PDE-5 inhibitor use described above. It is quite likely, however, that harm from ototoxic medications is occurring but is not appreciated, as such harm produces less obvious signs and symptoms and can accrue over longer periods of time.

Hearing impairment does not need to be severe to have a significantly detrimental effect on the lives of adults and children. It is therefore clear that any effective measures to prevent ototoxic hearing loss would be beneficial to cognitive function, social participation, workplace success, psychosocial health, educational success, and other measures of quality of life.

Efforts to prevent ototoxic damage would have important financial benefits. The average lifetime socioeconomic burden of hearing loss of any cause, in 2015 dollars, is estimated at $1.4 million for a pre-lingually deafened child, and $350,000 for each adult with acquired hearing loss[18]. And, given the educational consequences of even mild to moderate hearing loss caused by ototoxicity, federal and state governments may be motivated to promote regulations that limit harm to the ears. Under the Individuals with Disabilities Education Act, funding for assistive hearing devices in classrooms and audiological services is required, and Individualized Educational Programs must be developed for hearing-impaired students who qualify for special education services[10]. Thus, in addition to protecting the public from ototoxic drugs, governments could reduce

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[23] Bregman, C.L., Adler, R.R., Morton, D.G., Regan, K.S., & Yano, B.L. (2003). Recommended tissue list for histopathologic examination in repeat-dose toxicity and carcinogenicity studies: a proposal of the Society of Toxicologic Pathology (STP). Toxicologic Pathology, 31(2), 252-253.

[24] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research. (October 2015). Nonclinical safety evaluation of reformulated drug products and products intended for administration by an alternate route. Guidance for industry and review staff.

education costs, even for students with mild or moderate acquired hearing loss, by requiring better preventative measures against ototoxicity.

The goal of ototoxicity screening does not need to focus on the elimination of most, or all, ototoxic damage. Instead, simple awareness of the potential for hearing loss, tinnitus, and vestibular dysfunction would help clinicians and members of the public to make more informed decisions about what medications are prescribed and used.

If such awareness does lead to even subtle reductions in ototoxic damage, the benefits could still be significant. For example, it is believed that a relatively small (10 decibel) improvement in hearing thresholds could make a significant difference in an individual's ability to accurately perceive the clarity of speech that he or she is hearing, especially in a noisy environment[25]. Such an improvement could allow an individual to participate in social engagements or hear the voice of a grandchild or spouse. Thus, preventing even this degree of hearing loss through ototoxic screening and awareness would be quite worthwhile.

8. Conclusion

Ototoxic damage is cellular in nature, and therefore affects the fragile, microscopic structures of the inner ear while largely sparing the more robust and larger structures of the outer and middle ears. Hearing loss that results from ototoxicity is sensorineural rather than conductive, and is often associated with tinnitus. As such, treatment options are quite limited, making prevention of ototoxic cochlear damage more important.

The consequences of even mild or moderate damage from ototoxicity are significant for both children and adults. Such damage could be prevented or minimized by improved understanding and awareness, beginning with routine screening of drugs for ototoxic effects. Despite the fact that ototoxic side effects are very common among currently marketed drugs, there is little regulatory incentive for drug manufacturers to assess the ototoxic potential of new drug products. And, while routine ototoxicity screening should be a logical priority for drug manufacturers, it is unlikely that they can be relied upon to comprehensively test their products for such side effects. For example, one post-marketing publication reporting the overall safety, and hearing safety, of sildenafil (a PDE-5 inhibitor) was written by five authors, all of whom were consultants or employees of its manufacturer[26].

We therefore ask the FDA to take significant steps toward requiring the routine testing of new drug products for their potential to hurt the ears. We feel that the first, and most important, step to accomplish this goal would be issuing the attached guidance document, "Ototoxicity: Nonclinical Evaluation During Drug Development".

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[25] Campbell, K., Hammill, T., Hoffer, M., Kil, J., & Le Prell, C. (2016). Guidelines for auditory threshold measurement for significant threshold shift. Otol Neurotol 37, e263-e270.

[26] Giuliano, F., Jackson, G., Montorsi, F., Martin-Morales, A., & Raillard, P. (2010). Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J Clin Pract, 64(2), 240-255.

C. Environmental Impact

We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.

D. Certification

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Signature

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