PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS (PIHL)

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Guidelines for Adult Auditory Threshold Measurement for Significant Noise Induced Threshold Shift

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Introduction

At minimum, all clinical trials should meet all International Conference on Harmonization (ICH) guidelines for clinical trials (http://www.ich.org/). Currently no US Food and Drug Administration (FDA) guidance exists specifically for pharmacological intervention studies for hearing loss or tinnitus. However, reproducible, validated methodologies of the highest rigor must be employed. Test equipment, test environment, procedures, and personnel must meet all relevant American Speech-Language Hearing association (ASHA), American Academy of Audiology (AAA), American National Standards Institute (ANSI) standards and guidelines and military standards where applicable.

General Test Environment

Audiologic testing ought to be conducted in a testing environment meeting current ANSI standards, including annual inspection. Note that ANSI standards have different specifications for single and double walled sound booths for permissible external ambient noise levels. Levels both outside and within booths should be measured to verify compliance with ANSI guidelines.

Personnel

All study testing for hearing should optimally be performed by audiologists having at least a master's degree in audiology from a graduate program accredited regionally

and by ASHA. In addition, each audiologist must hold a current audiology license in those states where licensure applies. Certain study design elements, such as subject screening for further audiological follow-up testing or longitudinal study follow up, may warrant testing performed by technicians who are certified by the Council for Accreditation in Occupational Hearing Conservation (CAOHC) and under the ultimate supervision of an audiologist. The audiologists or technicians will be responsible for all testing and for maintaining all audiologic data files for all patients enrolled in the study. For other countries, testing should be conducted by the equivalent personnel in the host country recognizing that in other countries, trained audiometric technicians may be the most skilled and appropriate personnel delivering the audiologic standard of care in that country. Further, it is incumbent on the study team to assure that all staff responsible for audiological testing in foreign-speaking nations both understand the protocol and ensure that language barriers do not introduce study confounds.

Equipment Standards

Test equipment, test environment, and procedures must meet all relevant ASHA, AAA, ANSI and JHACO standards and guidelines in the United States or equivalent in other countries.

Calibration

To ensure accurate and reliable auditory threshold determination, at minimum, audiologic test equipment should include calibrated audiometers for the conventional frequency range of 0.25-8 kHz, otoscope, and immittance audiometry, test environment (minimum single walled sound booth), procedures, and personnel meeting all relevant ASHA, AAA, ANSI, and Joint Hospital Accreditation Commission (JHACO) standards and guidelines in the United States or equivalent standards appropriate to the test site country.

All audiologic testing must be conducted using an audiometer calibrated at least annually in a test environment meeting ANSI specifications. If immittance audiometry is included, then the immitance bridge must also be calibrated at least once annually (ASHA 1987).

Test Procedures for Pure Tone Threshold Testing

Regardless of study design, subject audiological exams ought to include a detailed history including any preceding noise exposure and the use of hearing protective devices (HPDs), and whether additional complaints of aural pain, fullness, pressure, or tinnitus are present. A physical examination including otoscopy needs to be conducted with the appearance of the ear drum and any defects or abnormalities of the external ear canal noted. Evidence of middle ear disease including tympanic perforation requires further medical evaluation by an otolaryngologist. An audiometric examination should include tympanometry, a non-invasive test of middle ear function, and conventional pure tone audiometry (air 0.5, 1, 2, 3, 4, 6, 8 kHz.; bone 0.5, 1, 2, 4

kHz); a behavioral test of conductive and sensorineural hearing loss should be completed.

Pure-tone air conduction threshold testing both at baseline and post-test two to three weeks after noise exposure, will be conducted utilizing the modified Hughson-Westlake procedure. Pure-tone air-conduction testing will be conducted at 0.5, 1, 2, 3, 4, 6, 8 kHz. Bone conduction testing will be conducted at .5, 1, 2, 4 kHz if the pure tone air-conduction threshold at that frequency is greater than or equal to 15 dB HL.

Pure-tone threshold testing should be conducted using the modified Hughson Westlake procedure (Carhart and Jerger 1959, ASHA 1987) as follows: Initial descent towards threshold is accomplished in 10-dB steps. Beginning with the first non-response, level is increased by 5-dB for each non-response, and decreased by 10-dB after each correct detection response. Threshold is defined as the lowest level at which two responses are obtained out of three presentations on an ascending run.

At the baseline visit, pure-tone air-conduction testing will be immediately repeated at 1 and 2 kHz to determine that the subject provides reliable responses. Responses will be considered reliable if retest thresholds at both frequencies do not exceed ± 5 dB of the previously obtained threshold response. This method of verifying threshold reliability for ototoxicity monitoring in clinical populations is based on Fausti, et al., 1999 and Campbell et al., 2003. The timing of the baseline and follow-up tests may vary by study. Clinically, for acute acoustic trauma inclusion studies, an individual presenting clinically with a complaint of hearing loss or tinnitus ought to be evaluated as soon as possible to determine the extent of the injury and provide a diagnosis and prognosis

Determination of PTS, TTS and Otoprotection

If a diagnosis of STS is made (see STS Definition paper), the subject should be counseled to reduce their noise exposure and be retested after 30 days from last noise exposure. Subjects with an STS should also undergo a final tympanogram screen to rule out middle ear pathology as a cause of the hearing loss. If they pass the tympanogram screen in both ears, they should be referred for a diagnostic audiologic follow-up exam. If they do not pass the tympanogram screen they will be referred for otologic check and then diagnostic audiological assessment.

If it is determined that a permanent threshold shift (PTS) has occurred, then the PTS must be recorded. Determination of work-related injury or hearing loss should be documented with relevant (i.e., OSHA, DOD) criteria and reported as required. The affected individual needs to be counseled on the importance of HPDs, on limiting their future noise exposures, and the potential for progressive hearing loss that could impair speech discrimination and result in permanent disability.

Study Design and Data Capture

Ideally, a computerized study database should be configured so that when the post-noise audiogram is entered in the database, criteria for hearing change will

automatically be calculated and flagged, so that the examiner can recheck the frequencies in question.

Experimental design consists of within-subjects serial testing in which baseline standard frequency audiograms (as outlined above) are initially acquired by comparing similar measures obtained at the end of the study period to the relevant pre-exposure measure, reliable noise-induced changes in pure-tone hearing threshold can be identified. Thus, subjects will serve as their own control for identifying hearing change.

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