Guidance for Industry

Upper Facial Lines: Developing Botulinum Toxin Drug Products

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2014
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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of therapeutic biological products, specifically botulinum toxins, for the temporary improvement in the appearance of upper facial lines, such as glabellar lines or lateral canthal lines (LCLs). This guidance addresses the FDA's current thinking regarding the overall development program and clinical trial designs of botulinum toxin drug products to support approval for an upper facial lines indication. The information presented is intended to help sponsors plan clinical trials, design clinical protocols, and implement and appropriately monitor the conduct of clinical trials. This draft guidance is intended to serve as a focus for continued discussions among the Division of Dermatology and Dental Products, pharmaceutical sponsors, the academic community, and the public.[2] Development plans should be discussed with the review division before embarking on trials to ensure that the clinical trial design meets defined objectives.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[3]

[1] This guidance has been prepared by the Division of Dermatology and Dental Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of botulinum toxin drug products.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

This guidance does not contain a discussion of nonclinical or chemistry, manufacturing, and controls (CMC) issues. For information concerning nonclinical and/or CMC issues, see the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* and the guidance for industry *For the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use.*

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Upper facial lines, also known as hyperdynamic lines or lines of facial expression, develop in the skin of anatomic areas (e.g., glabella, lateral canthal area) overlying specific musculature (e.g., corrugator, procerus, orbicularis oculi).

There is an increase in demand for aesthetic procedures to treat the progressive development of facial lines that are associated with the aging process. Injection of botulinum toxin to improve the appearance of facial lines is one of the most common aesthetic procedures performed.[4]

Several botulinum toxin drug products for the temporary improvement in the appearance of glabellar lines have received FDA approval, including onabotulinumtoxinA (2002), abobotulinumtoxinA (2009), and incobotulinumtoxinA (2011).

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

1. Early Phase Clinical Development Considerations

Trials to identify an appropriate (safe and effective) dose are an important component of phase 2 development for a botulinum toxin drug product. A dose-response trial conducted during the early phase of clinical development (e.g., phase 2 clinical trials) to assess safety and efficacy at a range of doses can help ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used and may identify some dose-related side effects. For additional information on the FDA's current thinking regarding dose response, see the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* and the guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

[4] Sadick, N, 2004, The Cosmetic Use of Botulinum Toxin Type B in the Upper Face, Clinics in Dermatology, 22;29-33.

and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.

For topical drug products, sponsors should address unique concerns such as inadvertent injection, unintended mucosal exposure, and unintended transfer of the drug product. A delivery system designed to reduce the risk of inadvertent injection should be considered early in the development process.

2. Drug Development Population

The trial population should be representative of the target population for which the drug product is intended for use in clinical practice (e.g., reflective of the age, race, and sex of the population that will be using it for an improvement in upper facial lines in the United States). The inclusion and exclusion criteria should be sufficiently broad to allow enrollment of a population that will be representative of that anticipated with proposed labeling (e.g., representative of real-world use).

Sponsors are required to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting.[5] Because upper facial lines are uncommon in the pediatric population, the sponsor may request a waiver for the requirement to submit a pediatric assessment in the pediatric study plan.

If a sponsor plans to conduct clinical trials outside the United States, the sponsor should consider factors that may affect the acceptability of such data for drug product approval in the United States. Sufficient information should be provided to demonstrate that data from clinical trials conducted outside the United States are applicable to and will predict the clinical outcomes in U.S. patients (see 21 CFR 314.106). We also refer the sponsor to the ICH guidance for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data* and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials*.

3. Efficacy Considerations

In general, two adequate and well-controlled trials are needed to establish safety and efficacy of a drug product that seeks an indication for the temporary improvement of upper facial lines. The sponsor is referred to the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

We recommend using both investigator-assessed and patient-reported outcome assessment tools to support the primary efficacy endpoint. We encourage the use of well-defined, valid, and reliable patient-reported outcome measures to assess the subject's perspective related to drug product effectiveness.

[5] See the Pediatric Research Equity Act (Public Law 108-155; section 505B(e)(2)(A) of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355B) as amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144).

See section III.B.9., Efficacy Endpoints, for a detailed discussion of endpoints and endpoint assessments.

4. Safety Considerations

The protocol should specify the methods to be used to obtain safety data during the course of the clinical trials. Generally, both adverse event information and safety laboratory data should be collected during clinical trials. All subjects should be evaluated for safety at the time of each trial visit or assessment, regardless of whether the investigational drug product has been discontinued. All adverse events should be followed until resolution, even if time on clinical trial would otherwise have been completed.

Botulinum toxin drug products present a unique set of safety concerns related to the potential for local and distant spread of toxin effect. Therefore, safety data related to this specific potential effect should be obtained through directed query and physical examination to evaluate for signs and symptoms of local and distant spread of toxin effect (see Appendix A). Assessment for effects on the neuromusculature should be performed for a sufficient duration post-treatment to capture late-onset events.

Sponsors should conduct repeat-dose trials to evaluate efficacy and safety after repeated administration of the investigational drug product for the improvement of upper facial lines. For drug products that seek an indication for upper facial lines in more than one anatomic area, drug product safety information would be needed for each area independently as well as for concomitant administration to more than one anatomic area, because adverse reactions related to local spread of toxin effect often will be specific to the anatomic area.

Drug products for the temporary improvement of upper facial lines have the potential for chronic intermittent use; therefore, sponsors should establish the long-term safety of the drug product in the proposed population at the proposed dose. Long-term controlled trial data are preferred over open-label extension safety data because of the difficulty in interpreting adverse events data in the absence of a concurrent control. The ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* provides advice regarding the number of subjects exposed and duration of treatment needed to inform the safety database. However, because upper facial lines are aesthetic indications and the risk-benefit assessment for this indication differs from that for indications such as blepharospasm, cervical dystonia, migraine, or spasticity, the minimum number of subjects described in ICH E1A may not be sufficient to allow assessment of the risk versus the benefit for the indications of upper facial lines, conditions with minimal morbidity. The size of the safety database may vary depending on the formulation and anatomic location to be treated. We recommend consulting the review division regarding this issue.

Sponsors should address the potential for immunogenicity of botulinum toxin, especially for a long-term treatment paradigm, and evaluate the effect of immunogenicity on the efficacy and safety.

B. Phase 3 Efficacy Trial Considerations

The protocol should describe the trial objectives, the target population, investigational drug product dosage and duration of treatment, the primary endpoints, and key planned statistical analyses. In addition, the trial design should support the proposed claims by taking into consideration the following factors.

1. Trial Design

In general, sponsors should conduct two randomized, double-blind, controlled trials to establish efficacy and safety. The preferred design should include a comparison to placebo or vehicle. In a placebo-controlled design, potential influences on the course of the condition other than those arising from the pharmacologic action of the investigational drug product can be controlled via randomization and blinding. The sponsor is referred to the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

2. Trial Population

The trial population should reflect the patient population that would be reasonably considered for treatment with the drug product, should the drug product be shown to be effective. It is important that the trial population not be made artificially narrow.

The past use of botulinum toxin drug products may affect the outcome with regard to both safety and efficacy and should be addressed in protocols for the temporary treatment of upper facial lines. In addition, the likelihood of unintentional unblinding could increase because individuals previously treated with botulinum toxin for upper facial lines may be more likely to determine whether they received the investigational drug product or placebo. If subjects are enrolled who have had previous treatment with botulinum toxin, sponsors should record this status at baseline to allow for a subgroup analysis to explore how previous exposure affects safety and efficacy.

To adequately represent the population of future use, the pivotal trials should enroll subjects with all levels of severity of facial lines who meet the inclusion criteria, including subjects at the upper end of severity.

We encourage enrollment of subjects with a diversity of Fitzpatrick skin types.

A sufficient number of subjects 65 years of age and older should be evaluated at the level of exposure (dose and duration) proposed for use to support conclusions regarding drug safety and efficacy in this population. Refer to the ICH guidance for industry *E7 Studies in Support of Special Populations: Geriatrics*.

3. Inclusion and Exclusion Criteria

Inclusion criteria should specify a minimum baseline level of condition severity.

Subjects with the following characteristics should be excluded from trials for the temporary improvement of upper facial lines:

- Concurrent or recent (e.g., within the last 6 months) use of any other botulinum toxin drug product
- Known immunization or hypersensitivity to any botulinum toxin serotype
- Anticipated need for treatment with botulinum toxin of any serotype for any reason during the trial (other than the investigational treatment)
- Any medical condition that may put the subject at increased risk with exposure to botulinum toxin including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other condition that might interfere with neuromuscular function
- Pregnancy or lactation

4. Concomitant Treatments

Sponsors should address in the protocol the use of other drug products that are intended for the treatment of wrinkles or facial lines, such as retinoids and fillers, for the temporary improvement of upper facial lines because concomitant use of these drug products may affect the outcomes. The protocol should define the concomitant therapy that is acceptable, and sponsors should record information on use of concomitant medications for a prespecified period before and during the trial. One option would be to exclude use of such drug products (such as retinoids and fillers) for an appropriate interval before trial initiation and for the duration of the trial (or at least up to the primary assessment time point).

5. Randomization, Stratification, and Blinding

Subjects should be randomized for receipt of the investigational drug product at enrollment. All trials should be multicenter, well-controlled, and double-blind. Randomization and blinding are important to minimize biases.

Efficacy assessments in the evaluation of drug products for the temporary treatment of upper facial lines have a certain level of subjectivity. In addition, the mechanism of action of botulinum toxin (paralysis or diminution of facial muscular activity) may lead to unblinding even in subjects who do not meet objective criteria to be considered responders. Therefore, it is important that the protocol documents steps to maintain double-blinding (subject and assessor) to the extent possible. (See section III.B.11., Endpoint Adjudication.)

If the effects of treatment are expected to differ substantially among different groups of subjects (e.g., baseline condition severity, prior botulinum toxin use), it may be desirable to stratify at randomization on that factor.

6. Specific Populations

The currently approved botulinum toxin drug products' labeling indicates that there are no adequate and well-controlled trials in pregnant women.

As noted in section III.B.3., Inclusion and Exclusion Criteria, pregnant subjects and nursing mothers should be excluded from trials of botulinum drug products for the temporary treatment of upper facial lines.

With regard to pediatric subjects, as noted in section III.A.2., Drug Development Population, upper facial lines are uncommon in the pediatric population; the sponsor may request a waiver for the requirement to submit a pediatric assessment.

With regard to geriatric subjects, as noted in section III.A.2., Drug Development Population, a sufficient number of subjects 65 years of age and older should be evaluated at the level of exposure (dose and duration) proposed for use to support conclusions regarding drug safety and efficacy in this population.

7. Dose Selection

Clinical trials to identify an appropriate (safe and effective) dose are an important component of phase 2 development for a botulinum toxin drug product. (See section III.A.1., Early Phase Clinical Development Considerations, for a more detailed discussion of dose-ranging.) Assessment of the safety and efficacy of repeat treatment should be included in the development program.

8. Choice of Comparators

See section III.B.1., Trial Design, for a discussion of comparators.

9. Efficacy Endpoints

a. Assessment measures

Measurements at maximum contraction should be used to assess the efficacy of botulinum toxin drug products to demonstrate the paralytic effect of the botulinum toxin. This is needed to justify the use of botulinum toxin in a drug product intended for aesthetic use (i.e., to show that the toxin has a paralytic effect on muscle and therefore is necessary for drug product effectiveness).

The recommended co-primary efficacy endpoints should be based on *well-defined and reliable*[6] clinician-reported and patient-reported assessments that are developed to measure the critical outcomes that contribute to a conclusion of overall success or failure.

[6] See 21 CFR 314.126.

Instrument development for the subject assessment of line severity in the targeted area should be based upon qualitative research conducted in the target patient population to ensure the instrument content is appropriate for the targeted patient population to be studied in clinical trials.[7] Similarly, clinician input is valuable in the development of well-defined and reliable clinician-reported outcome measures. Upper facial lines are aesthetic conditions; therefore, the endpoints should include an assessment of the effect of the drug product on outcomes that are important to the targeted patient population. If an adequate patient-reported or clinician-reported instrument is not available for assessment of upper facial lines, the new instrument development process should begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol.

For both investigator- and subject-assessment instruments, the scales should be ordinal, static (meaning the evaluation is of the current severity rather than a change in severity relative to a previous time point), and comprised of a limited number of categories or grades. Each category should represent a distinct and clinically meaningful gradation of the condition, and should be defined by a noncomparative, nonoverlapping, clinically relevant morphologic description to minimize interobserver variability. The category of "none" or zero should represent true absence of the condition. A photonumeric guide with examples of each grade can be provided to investigators and subjects as an assessment aid to facilitate optimal inter- and intrarater reliability. The same scale should be used throughout the trial, including at enrollment, at the primary efficacy time point, and at time of assessment for loss of effect. To provide internal correlation, the subject's self-assessment (SSA) and the investigator's assessment (IA) scales should contain the same number of categories.

The degree of improvement determined to be clinically meaningful (and therefore appropriate for regulatory decisions) should be determined during instrument development and should be discussed with the FDA before trial initiation. Statistically significant differences between comparator regimens may not be sufficient for demonstrating benefit if response to treatment has not been shown to be clinically meaningful.

For LCLs, efficacy should be based on bilateral results (both sides of the face) rather than results from each side of the face counted separately. Success should be determined at the subject level such that a subject would be considered a success only if both left and right side assessments meet the success criteria.

We also encourage sponsors to discuss endpoint measures with the FDA in the early planning phases of clinical development. For novel outcome measures, we recommend that the sponsor submit a draft instrument (complete instrument and description of plans for the development and testing of the instrument) to the investigational new drug application for FDA review as early as possible in the development program.

[7] For recommendations on how to determine whether a clinical outcome assessment is well-defined and reliable, refer to the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

b. Endpoints

For each anatomic region, the primary efficacy endpoint should be based on responder rates defined by an IA scale at maximum contraction and an SSA scale at maximum contraction. Maximum contraction should be defined based on the targeted area (e.g., maximum frown for glabellar lines, maximum smile for LCLs).

As discussed in section III.B.9.a., Assessment measures, assessment at maximum contraction is needed to show that the toxin has a paralytic effect on muscle and therefore is necessary for the drug product's efficacy. A drug product containing botulinum toxin that fails to demonstrate an effect at maximum contraction might have difficulty showing a favorable risk-benefit profile that is at the heart of regulatory decision making. In addition, demonstration of efficacy at both extremes (maximum contraction (which represents the worst appearance of upper facial lines with maximum load on the muscle) and at rest (which represents the best appearance of upper facial lines with the least load on the muscle)) allows one to impute benefit when the face is in dynamic motion (variable load on the muscle).

The clinician's and subject's assessments of line severity at maximum contraction should be used at baseline to establish enrollment eligibility. There should be a sufficient score at enrollment on each instrument such that a clinically meaningful response can be observed.

Success should be defined as achievement of a score of 0 or 1 *and* a two-grade improvement from the baseline, on both the IA and the SSA scales concurrently, to ensure clinical significance. Because it may be possible to move to an adjacent category on the assessment scale with only a small level of improvement, a one-grade change may not represent a clinically meaningful intrasubject change.

Secondary endpoints should be clinically relevant, limited in number, and adjusted for multiplicity to control the type I error rate. Assessments at rest (as opposed to at-maximum contraction) provide supportive evidence of efficacy and may be useful as secondary endpoints.

10. Trial Procedures and Timing of Assessments

Clinical trial duration should be based on the onset of action of the drug product and should be of sufficient length to assess the durability of therapy benefits. The clinical development program should include a trial that incorporates repeated doses for at least 1 year to assess for the safety of repeat doses.

Sponsors should also provide adequate evidence to support the selection of the time point(s) for assessment of the primary efficacy outcome. The time point for assessment of the primary outcome should be at or after the onset of the full effect of the botulinum toxin drug product.

Sponsors should evaluate duration of effect with a clinically and statistically meaningful approach. Assessment measures for duration of effect should be the same as for the primary efficacy endpoint. Assessment of the duration of effect should reflect the time period for which a clinically meaningful proportion of subjects maintain response.

11. Endpoint Adjudication

Unblinding is a significant concern in trials for botulinum toxin drug products for the improvement in the appearance of facial lines. Therefore, results of review of photographs at maximum contraction by a masked, independent committee of experts using the investigator's static scale should be provided as a secondary endpoint.

12. Statistical Considerations

Sponsors should address general statistical principles (e.g., randomization, blinding, prespecification, multiplicity control of type I error) in trials for botulinum toxin drug products for the improvement of upper facial lines in the same way as in trials for other medical drug products. However, some statistical issues may need special consideration in clinical trials for upper facial lines.

Sponsors should describe the randomization scheme, including the randomization ratio, and any stratification factors or block size, along with adequate details about how subject assignment will be carried out. Double-blind trials should be conducted whenever possible because of the subjective nature of the efficacy assessments.

Clinical trials should be adequately powered for the primary efficacy endpoints. Sample size calculations are typically based on type I error, power, and expected outcomes. In some cases, there may be a need to power the trial for safety as well, so that important adverse reactions can be adequately characterized, because there may be a low tolerance for serious or bothersome adverse reactions associated with aesthetic use drug products.

If the trial is designed with more than one primary endpoint, the protocol should specify the methodology that will be used to control the overall type I error rate. The protocol should include a plan for adjusting for multiplicity in cases with more than one primary or secondary endpoint. If the primary efficacy endpoint is a success rate based on meeting multiple criteria for achieving response, then the criteria for achieving success should be defined (e.g., achieving a score of 0 or 1 and at least two grades reduction on both the IA and SSA scales).

Sponsors should specify the statistical methods to be used for the analysis of all endpoints. They should be appropriate for the type of data collected. The statistical methods should be specified with sufficient details, including any model terms, covariates, or stratification factors. If there are particular subgroups of interest, subgroup analyses should be planned in the protocol. The subgroup analyses should be designed so as to maintain control of the type I error rate.

The primary analysis population should be the intent-to-treat population defined as all subjects randomized and dispensed the investigational drug product. The protocol should prespecify a plan for handling missing data, along with the justification for any assumptions needed for the imputation method. The protocol should also prespecify a plan for sensitivity analyses regarding the handling of missing data.

Sponsors should describe the follow-up visit schedule. Long-term follow-up may be needed to assess duration of effect. Protocols should include plans to minimize loss to follow-up, because subjects may not be motivated to return for follow-up after receiving treatment or may comply with only some of the post-treatment visits.

Because botulinum toxin drug products generally are administered by the investigator, investigator technique or skill may affect the results. Trials should be designed to enroll a sufficient number of subjects per center so that investigator-to-investigator variability and treatment-by-center interactions can be adequately assessed.

13. Accelerated Approval (Subpart H) Considerations

Upper facial lines are not a "serious or life-threatening condition"; therefore, accelerated approval is not appropriate.

14. Risk-Benefit Considerations

Assessment of risks and benefits involves an assessment of the effect of the botulinum toxin drug product on the condition of upper facial lines. The primary efficacy analysis should demonstrate a statistically significant result and the measured clinical effect of the botulinum toxin drug product should be clinically meaningful. Toxicities related to the pharmacologic effects of the botulinum toxin drug product (e.g., potential for distant spread of toxin effect) also should be considered as part of this overall risk-benefit assessment.

C. Other Considerations

1. Risk Management Considerations

Botulinum toxin drug products for the treatment of upper facial lines are prescriber-administered. Patients need to be aware of the potential safety issues that have arisen with the use of these drug products to make an informed decision as to whether they wish to receive this therapy. For this reason, a Medication Guide should be provided to each patient before treatment after approval.

2. Pharmacokinetic/Pharmacodynamic Considerations

Currently, it is not possible to detect botulinum toxin in the peripheral blood following intramuscular injection at doses recommended for use for approved drug products for upper facial lines because of the limits of available analytical technology. The need for pharmacokinetic assessment may be reevaluated as new technologies become available.

3. Special Investigation Considerations

For topical products, dermal safety studies with the final to-be-marketed drug product should provide information regarding cumulative irritancy, contact sensitization, phototoxicity, and photo-contact allergic potential.

4. Labeling Considerations

The labeling for botulinum toxin drug products should include a boxed warning that describes the risk of distant spread of toxin effect as well as a Medication Guide to help patients better understand the potential risks associated with these drug products.

The labeling also should include a subsection in the WARNINGS AND PRECAUTIONS section that warns that the potency units of one botulinum toxin drug product are not interchangeable with other preparations of botulinum toxin drug products. Recommended frequencies for retreatment should be included in the DOSAGE AND ADMINISTRATION section.

The INDICATIONS AND USAGE section of labeling for botulinum toxin drug products intended to improve upper facial lines should identify the anatomic location of the lines and the underlying musculature involved in their development. The nonpermanent nature of the treatment should be conveyed.

Representative examples of indication statements for a botulinum toxin drug product intended to improve upper facial lines can include:

- The temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and procerus muscle activity in adults

- The temporary improvement in the appearance of mild to moderate LCLs associated with orbicularis oculi activity in adults

APPENDIX A

The following adverse events potentially suggestive of *distant spread of toxin*, and therefore of special interest, include:

accommodation disorder
areflexia
aspiration
blurred vision
botulism
Bradycardia
bulbar palsy
constipation
cranial nerve palsies
cranial nerve paralysis
diaphragmatic paralysis
diplopia
dry mouth
dysarthria
dysphagia
dysphonia
dyspnea
extraocular muscle paresis
eyelid function disorder
eyelid ptosis
facial palsy
facial paresis
fourth cranial nerve paresis
hemiparesis
hypoglossal nerve paresis
hyporeflexia
hypotonia
monoparesis
muscular weakness
paralysis
paralysis flaccid
paralytic ileus
paraparesis
paresis
paresis cranial nerve
peripheral nerve palsy
peripheral paralysis
pelvic floor muscle weakness
pneumonia aspiration
pupillary reflex impaired
quadriparesis
respiratory arrest
respiratory depression
respiratory failure
speech disorder
third cranial nerve paresis
trigeminal nerve paresis
urinary retention
vocal cord paralysis
vocal cord paresis