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Urinary Incontinence in Women— Practical Implications in Clinical Development

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With the predicted growth of the global aging population, there is projected an increased public health burden for the management of urinary incontinence. Despite growing public awareness and less de-stigmatization, hundreds of ongoing clinical trials and numerous approved pharmacologic products, medical devices and surgical procedures for the management of urinary incontinence, there remains an unmet medical need in adequately addressing urinary incontinence. Although it disproportionately affects women, it also occurs in men, and women across the age spectrum. There is no lack of regulatory guidance surrounding the urinary incontinence drug and device product development landscape as is evident by the U.S. Food and Drug Administration's Guidance for Industry and Food and Drug Administration Staff Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence (2011) and the European Medicines Agency's Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence (2013), which respectively address device and pharmaceuticals. Both guidance documents addresses incontinence definitions, study design and objectives with remarkable consistency. This paper discusses the different types of urinary incontinence, protocol design, efficacy endpoint considerations and trial execution considerations that present both challenges and opportunities for urinary incontinence product development.

URINARY INCONTINENCE BACKGROUND AND INDUSTRY

Urinary incontinence is defined by the International Continence Society as the involuntary loss of urine that represents a hygienic or social problem to the individual. Urinary incontinence affects approximately 10 to 13 million people in the United States and 200 million people worldwide. The cost of treating urinary incontinence in United States is \$16.3 billion, 75 percent of which is spent on treatment of women. While the etiology of urinary incontinence can vary, including dysfunction of bladder, sphincter and or pelvic floor, the etiology is often unclear even with a detailed patient history and physical examination. Urinary incontinence increases with age and as the global population ages, urinary incontinence will become an increasing public health burden as it is often a chief reason for

institutionalizing elderly people in nursing homes and other non-acute care facilities.

Urinary incontinence is more common in women compared to men. Prevalence rates in women begin to peak at menopause with rates close to 80 percent in women between 49-60 years. Approximately 25 percent of premenopausal women and 40 percent of postmenopausal women report involuntary leakage of urine. However, women aged 18-40 years are also affected, but at much lower rates (10 to 40 percent). Although a common condition, urinary incontinence is often underreported and undiagnosed even with increased awareness due to social media and direct-to-consumer advertising of urinary incontinence pharmaceutical and self-care products targeting women.

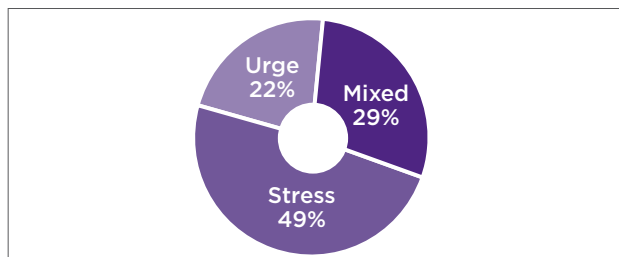
The overall prevalence of urinary incontinence in men is much lower than women — three to 11 percent — with urge incontinence being the predominant type of incontinence experienced by men, usually related to bladder outlet obstruction because of prostate enlargement. The prevalence of stress incontinence increases with age, in men and women, but at a comparable rate. In contrast, in the incidence in stress incontinence for women increases with age, whereas stress incontinence becomes relatively rare in men.

The two main types of incontinence are stress (with effort or exertion) and urge incontinence. The term mixed incontinence refers to the concomitant appearance of stress and urge incontinence.

The International Continence Society (ICS) has published definitions at symptom level for the different forms of incontinence in adults:

- Stress urinary incontinence (SUI): is the complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.
- Urge urinary incontinence (UUI): is the complaint of involuntary leakage accompanied by or immediately preceded by urgency.
- Mixed urinary incontinence (MUI): is the complaint of involuntary leakage associated with urgency and with exertion, effort, sneezing or coughing (SUI and UUI).

Fig. 1.1 Spectrum of Voiding Dysfunction



“Pharmacotherapy for Overactive Bladder—Rationale for Treatment Choice” presentation by David A. Ginsberg, MD, Assistant Professor of Urology, USC Keck School of Medicine, slideshare presentation

URINARY INCONTINENCE CLINICAL TRIALS

Defining the target patient population for urinary incontinence (UI) clinical trials that assess the safety and effectiveness of pharmacologic/medical treatment or surgical intervention is a major challenge when designing a study. The respective UI guidances from the U.S. Food and Drug Administration (FDA) on incontinence devices and the European Medicines Agency (EMA) on medicinal products, both detail the rationale for defining the optimal target patient population that addresses the heterogeneity of patients with UI, the subjectivity and variability of outcomes measures and the significant placebo effect associated with trial procedures, interventions and outcomes measures.

When defining a broad versus narrow target study patient population for a clinical trial, several considerations must be made, including:

- Designing the study to enroll a broad patient population potentially increases the enrollment rate, allowing the drug, procedure or device to be studied over a wide range of patients
- Broadly defining the patient population can also result in the enrollment of patients with a variety of confounding factors, which can add significant variability and negatively affect the data analysis
- Defining the patient population narrowly may result in a homogeneous population that is easier to analyze because of smaller sample size and less variability in response to treatment and minimal placebo effect
- Narrowing the patient population could also slow the rate of enrollment and restrict the product/device labelling
- Defined age parameters also included in the protocol inclusion/exclusion criteria, for example, more than 18 years of age to a defined upper age range limit, such as 85 years. Other factors to consider include:
 - Stratifying for age to have an equal distribution of age and gender subjects across treatment arms

- Including older patients, specified as 65-74, 75-84, and more than 85 years of age in Phase III studies in sufficient numbers to permit evaluation of efficacy and safety in the older population

As it is difficult to separate prostate-related symptoms in men from incontinence not related to obstruction, it is generally preferred that men and women are investigated/analyzed separately. Further considerations include:

- If separate studies are not performed for males and females, the study should be stratified for gender
- Both gender subgroups should be analyzed separately

PROTOCOL DEFINITIONS OF OVERACTIVE BLADDER, SUI, MIXED INCONTINENCE

Most working definitions of UI are based on the ICS definitions at symptom level for the different forms of incontinence in adults:

- It is recommended to primarily include patients with “pure” stress or urge incontinence in studies of stress or urge incontinence
- It is often necessary to include patients with mixed incontinence in both kinds of studies; for example, some protocols specify mixed incontinence — either “urge” or “stress” predominant — are included as a defined percentage of study subjects
- It is important that the type of incontinence (stress, urge, etc.) being studied is the major complaint of the patient
- Disease severity should be clearly defined using validated grading systems to ensure that the target population is adequately reflected in the study population
- Objectively measured severity of incontinence that reflects the targeted patient population, such as:

- Minimum baseline pad weight as measured by a one-hour pad weight test or three 24-hour pad weight tests
- Minimum average number of baseline incontinence episodes per day as determined on a three-day or seven-day voiding diary (due to the high inpatient variability associated with UI, of a seven-day voiding diary is usually recommended during the pre-treatment evaluation)
- The protocol should specify that subjects meet the predefined severity level for study inclusion on each assessment
- Prior incontinence history including duration and severity of incontinence, prior treatments or surgery for incontinence:
 - Studies for more aggressive investigational devices should specify longer trial periods of conservative therapies, for example, six to 12 months of failed therapy prior to enrollment
 - General medical history specifying comorbidities and potentially confounding conditions, such as neurologic conditions and significant pelvic organ prolapse

CONSIDERATIONS FOR USE OF URODYNAMIC TESTING

According to FDA guidance, the use of urodynamic measurement as a primary endpoint to test effectiveness has the advantage of being objective, standardized and less subject to variability. But it also has the potential disadvantages of being not meaningful to patients, invasive and “specific to categories.”ⁱ

Urodynamic testing is also recommended at pretreatment evaluation to confirm diagnosis of the different type of UI, which is also confirmed by an EMA guideline “... in addition to history and clinical examination and to micturition diaries, to confirm the diagnosis”ⁱⁱ

Urodynamic measurements are also used endpoints across all phase of clinical development. These parameters can be useful supportive data in the evaluation of the study outcome or to understand reasons for lack of responses. On the contrary of the FDA-listed advantages, such as objective and standardized, the EMA guideline warns about “significant limitations to this type of studies: interpretation is subjective and urodynamic data are poorly reproducible”.¹

It is therefore evident that lack of standardization is perceived as a substantial risk and that consensus is required by at least two, preferably three, qualified and independent reviewers.

All guidelines on UI recommend the following as the routine first steps in the evaluation of a patient with urinary incontinence:

- Clinical history including voiding patterns, incontinence medication history, previous behavioral interventions and surgical procedures
- Urinalysis and urine culture
- Detailed physical examination including pelvic, rectal, prostate, observation of the patient’s gait, evaluation of sacral sensation and reflexes and identification of other neuro-urological findings
- Validated symptom and/or bother scores
- Noninvasive urodynamic testing for patients with lower urinary tract symptoms: frequency/voiding chart (FVC) or bladder diary (BD), uroflowmetry and post-void residual (PVR) should be done prior to performing invasive urodynamics

Invasive urodynamics testing involves catheterization of the bladder through the urethra, the placement of a rectal catheter to measure abdominal pressure and often needle electrodes for sphincter electromyogram (EMG). These procedures are uncomfortable, often embarrassing to patients and carry the risk of pain, hematuria, infection and possible urinary retention. Video-urodynamic studies incorporate fluoroscopic imaging while

performing cystometry. Although these procedures can be uncomfortable and pose risks to patients, the information gathered from urodynamic testing is invaluable and includes assessments of the bladder wall, bladder neck, external urinary sphincter coordination and vesicoureteral reflux.

Although invasive tests are usually used before surgery, none of the current guidance specifically requires invasive urodynamic testing prior to pharmacologic, behavioral or surgical intervention for incontinence, and there is little evidence to prove that they improve the choice of intervention or treatment outcome. There is also a considerable amount of inter- and intra-tester and site variability in performing urodynamic testing.

To increase the quality of individual clinical and research urodynamic testing, the working group initiated by the ICS standardizations steering committee has updated the International Continence Society Standard: Good Urodynamic Practice that was initially published in 2002. The ICS standardization working group updated the ICS’s Good Urodynamic Practice standard. In 2016, the ICS defined terms and standards for the practice of urodynamics labs in general, for the individual practice of quality control during and after cystometry, and for pressure-flow analysis.

EXPECTED HIGH PLACEBO EFFECT

Placebo response rates in lower urinary tract symptoms (LUTS) are high, congruent with the more subjective nature of LUTS severity outcome measures. Trials assessing subjective outcomes generally record higher placebo effects than those using objectively measurable outcomes. A strong behavioral component is present because the commonly used voiding diaries make the patients aware of their micturition habits. Inclusion of objective outcome measurements and appropriate run-in periods may contribute to disentangling genuine treatment from placebo effects, unless alternative study designs and/or means are found and implemented for a successful higher reduction of the placebo effect.

The five most commonly reported parameters are changes in:

- Incontinence episodes per day
- Micturition episodes per day
- Urgency episodes per day
- Mean volume per micturition
- Maximum cystometric capacity

Relating to placebo effects reviewed in overactive bladder (OAB) trials with strong behavioral components described, among those five parameters urgency seems to remain unaffected, as this parameter is spontaneous and subconscious and less amenable to training.

DEFINITION OF ENDPOINTS

The FDA guidance is clear that the most appropriate endpoint for selection in any study depends on the condition and target population. For this purpose, the FDA also provides a list of endpoints for UI with advantages and disadvantages. Ultimately one or both following primary endpoints are recommended by the agency after a careful comparison of benefits and limitations of various endpoints. This comparison that is consistent with “a consensus effort sponsored by the World Health Organization”¹:

- Reduction in urine leakage, as assessed by pad weight at the follow-up visit (relative to baseline)
- Reduction in the number of incontinence episodes per day at the follow-up visit (relative to baseline)

The reduction in urine leakage is recommended to be assessed by a pad weighting test, using standardized techniques. The most meaningful measure of success is dryness, which is defined as:

- Pad weight increase of less than 1 gram for the one-hour pad weight test
- Pad weight increase of less than 1.3 grams for the 24-hour pad weight test

“The most meaningful measure of success for any urinary incontinence treatment is dryness, which is the outcome that patients ultimately seek.” FDA¹

Based on the agency experience reviewing UI studies, it is recommended to define a clinically meaningful level of improvement as a pad weight reduction greater than 50 percent from baseline.

The reduction in the number of incontinence episodes should be assessed using a standardized voiding diary to daily and chronologically measure:

- Fluid intake
- Incontinence episodes with associated activities and perceived level of urgency and severity per each incontinence episode
- Pad usage
- Normal voiding episodes and measured volume

Reporting the average number of episodes per day over seven consecutive days is recommended to reduce within-patient variability.

When using the reduction in the number of incontinence episodes as assessment, dryness is defined as zero episodes per day and, in this case a clinically meaningful level of improvement is defined as a reduction greater than 50 percent in the number of incontinence episodes per day.

Composite endpoints (pad weight and number of incontinence episodes) can be measured.

Secondary endpoints can be used to provide additional characterization of the treatment effect. Those recommended in the guidance are quality of life, sexual function, patient satisfaction and urodynamic assessments.

Although the FDA guidance doesn't discriminate in the selection of endpoints on the phase of the study, a different approach is taken in the EMA guideline that clarifies expectations between therapeutic exploratory, dose-finding (Phase II) studies and confirmatory (Phase III) studies.

In Phase II therapeutic confirmatory studies, it is expected that the primary endpoint is a urodynamic assessment parameter, which is appropriate for the intended condition with an exception for OAB where a clinical endpoint should be used. Clinical endpoints should be used as secondary endpoints, per the same recommendations that are valid for Phase III studies.

For Phase III confirmatory studies, changes in quantitative symptom measures are required, but include a patient's perception in the analysis.

- A single, objective endpoint, for example, the number of incontinence episodes
- A design with two co-primary endpoints, where the second is strongly related to the patient's perceived effect or quality of life (QoL)

Contrary to the possibility envisioned in the FDA guidance, the EMA guideline discourages the use of composite endpoints.

The description of endpoints in the EMA guideline resembles the FDA guidance, with emphasis on standardization (e.g., pad weight test), and especially quality-of-life measurements that are considered "extension of an evaluation of efficacy."ⁱⁱ

A review was conducted of all UI studies currently listed in ClinicalTrials.gov, to check the reported primary outcome and any differences among phase and/or investigational product.

Table 2.1 UI - distribution of study by intervention

Intervention	Biological	Device	Drug
Number	22	27	145
Percentage	11%	14%	75%

*The query structure—
urinary incontinence | Interventional Studies | Studies with Female Participants | Phase 1, 2, 3, 4, 0 | Industry—
was used.*

The query returned a total number of 237 records. 42 records were discarded as related to indications not relevant to UI, or with primary outcome not reported. 194 records were left for analysis. Interventions, biological, drug or device, were distributed as below:

From an intervention perspective, studies in drugs represent more than 75 percent of the total studies. Biologicals (predominantly Botulinum toxin) and devices shared similar numbers.

Differently, from an indication (or condition) perspective:

Table 2.2 UI - distribution of studies by condition

Condition	N of studies in indication	Percentage (Total)
OAB	120	62%
Stress Urinary Incontinence (SUI)	36	18%
Urinary Incontinence, generic (UI)	17	8%
Urge Urinary Incontinence (UII)	5	3%
Neurogenic Bladder	6	3%
Nocturia	5	3%
Other*	5	3%

**Detrusor function, overactive, LUTS, multiple sclerosis*

OAB is the indication most frequently studied with 120 studies (62 percent) listed, followed by SUI with 36 studies (18 percent) executed. Both indications together cover 80 percent of all studies executed in UI indications, at the time of publication.

Table 2.3 UI - distribution of studies by phase*

Phase of Study	N of studies in phase	Percentage (Total)
Phase I	6	3%
Phase II	46	24%
Phase III	90	46%
Phase IV	52	27%

*Phase of clinical development (Phase I, Phase II, Phase III) of drugs is not applicable for devices, but used for simplification

Products in Phase III of clinical development represent about 50 percent of all studies in UI. Phase II and Phase IV studies cover, respectively, another 25 percent with three percent Phase I studies.

The different distribution obtained by intervention, condition studied and phase shows that most executed studies are drug studies, in the OAB indication and Phase II to IV.

While the FDA guidance doesn't apply different recommendations between pilot and pivotal studies phases, the EMA guideline expects that:

Table 2.4 UI - selected endpoints by phase - drug studies

Phase of study	N of studies in phase (%)	IEF* (%)	PROs** (%)	Urodynamic Assessments (%)
Phase I	5	2 (40%)	3 (60%)	2 (40%)
Phase II	40	38 (95%)	23 (58%)	6 (15%)
Phase III	80	70 (88%)	45 (56%)	8 (10%)
Phase IV	42	26 (62%)	37 (88%)	3 (7%)

*IEF = Incontinence episode frequency

**The definition of PRO (patient-reported outcome) is preferred to quality of life (QoL) to reflect the variety of tools reported.

- Urodynamic measures are assessed as the primary endpoint for Phase II, therapeutic exploratory studies, with clinical endpoints as secondary.
- Clinical endpoints are assessed as primary endpoints for Phase III, confirmatory trials, with patient-reported outcome (PRO) strongly recommended as co-primary

It was therefore interesting to investigate the selected endpoints as reported in clinicaltrials.gov by phase.

When assessing the distribution of endpoints by phase in drug studies, the number of incontinence episodes is the preferred clinical endpoint reported in almost all studies in Phase II and more than 85 percent of studies in Phase III, followed by PROs. In Phase IV studies, PRO assessments are the most frequent assessments used.

Interestingly, only a few urodynamic assessments are reported. Indeed, urodynamic assessments are more frequently reported in early Phase I and II, which is compatible with the aim to elucidate mechanism of action, but they are also present in Phase III and Phase IV studies with no substantial differences among phases, apart from Phase I. Various reasons could justify this lack of substantial difference, including the time of introduction of the EMA guideline in 2013 (listed studies are not filtered by start date), drugs that were thoroughly investigated early in development and their mechanism of action does not require further assessments, and different regulatory requirements between FDA and EMA.

Table 2.5 UI – selected endpoints by phase – device studies

Phase of study*	N of studies in phase (%)	IEF* (%)	PROs** (%)	Urodynamic Assessments (%)
Ph I	1	0	1 (100%)	0
Ph II	6	2 (33%)	5 (83%)	0
Ph III	10	6 (60%)	6 (60%)	0
Ph IV	10	4 (40%)	7 (70%)	0

* For comparison purposes the same distribution in phases of clinical development used for drug was kept, even though these phases are not applicable for devices.

The main difference when comparing device with drug studies, is the lack of any urodynamic assessment reported among the study endpoints and the overall preference for PRO assessments. It should be noted that additional safety endpoints were reported typical for device studies, as device-related effects, but also pad weight that was described in the FDA guidance recommended endpoints, and none were found referenced (as endpoint) in drugs.

In summary, when the selection of endpoints in UI studies is reviewed by phase and intervention, e.g., drug or device, the number of incontinence episodes is the endpoint of choice, along with PRO assessments that are also more frequent at later stages of clinical development.

The importance of urodynamic assessments in early phases of development is emphasized in the EMA guideline, yet urodynamic assessments are scarcely represented as endpoints in drug studies and weren't found in device studies. When urodynamic assessments in Phase I studies are expressed as percentages (40 percent) a substantial difference can be appraised against Phase II/III studies (average equals 12.5 percent), but due to the relatively small sample size of Phase I studies with drugs (5/167, three percent), this isn't considered a large enough sample to support this difference.

UI Guidelines Highlight— A Device (FDA) Versus Drug (EMA) Comparison

Medical device and drug development in UI are covered by guidance and guideline, respectively issued by the FDA and the EMA:

The Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence, guidance from the FDA, was issued by the Center for Devices and Radiological Health (CDRH) in 2011. EMA released the Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence in 2013.

Despite the difference in structure of the table of contents, there are common criteria described in the two documents, which set the expectations of the regulatory agency in demonstrating safety and efficacy of drugs and devices for the treatment of UI indications.

Table 2.6 FDA Device Guidance vs EMA Drug Guideline UI Comparison

CRITERIA	FDA DEVICE UI GUIDANCE (2011)	EMA DRUG UI GUIDELINE (2013)	HIGHLIGHTS
INDICATIONS	<p>Clinical indications:</p> <p>Stress incontinence, urge and mixed are described, and hypermobility, intrinsic sphincter deficiency (ISD), overflow incontinence, functional and continuous incontinence</p>	<p>Diagnosis:</p> <p>Stress incontinence, urge incontinence, mixed Incontinence are described, including overactive bladder syndrome</p>	<p>There is no reference in the FDA guidance about OAB syndrome, and in the EMA guideline there is no reference about hypermobility, ISD, overflow, functional and continuous incontinence.</p> <p>SUI, UUI and MUI are described indications in common.</p> <p>Of note, the EMA guideline separates the differentiation between signs and symptoms</p>
EARLY STUDY(IES) RECOMMENDATION(S)	<p>Pilot study recommendations particularly for surgical procedure studies:</p> <p>Initial study is recommended to minimize the risk to subjects and gain experience in the use of device(s). This is also intended to gain valuable information to identify eligible population and meaningful endpoints for next pivotal study(ies)</p>	<p>Urodynamic and structural studies:</p> <p>Urodynamic Phase (I-) II studies can elucidate the mechanism of action. They may help identifying target population, dose and endpoints for Phase II and Phase III studies</p>	<p>Both documents stress the importance of early studies to better define target population and the choice of endpoints for further development phase (e.g., pivotal, Phase II and III).</p> <p>Important and typical for device studies the need to “gain experience in the use of device” and “minimize the risk to subjects” especially for invasive devices, as devices are all class II/III (apart from class I protective garments) in this indication.</p>
STUDY DESIGN	<p>Randomization and control:</p> <p>Randomized, controlled study design can overcome most of the challenges inherent to UI studies. When designing a randomized, controlled study, it is recommended to select an appropriate control therapy particularly when evaluating a device and or surgical procedure. Typically, the current standard of care for the target patient population represent the most clinically meaningful choice of control</p>	<p>Design:</p> <p>Parallel group design, including one placebo arm, is recommended.</p>	<p>Blinding could be problematic in device trials, and use of placebo (sham) devices for their ethical implications in testing high-risk devices, involving surgical procedures in cases where single- and double-blind designs are not feasible.</p> <p>In cases where single- and double-blind designs are not feasible,</p> <p>It is usually possible to use a blinded third-party evaluator for the evaluation of certain outcome measures</p>

CRITERIA	FDA DEVICE UI GUIDANCE (2011)	EMA DRUG UI GUIDELINE (2013)	HIGHLIGHTS
STUDY ENDPOINTS	<p>Study endpoints:</p> <p>The primary safety and effectiveness endpoints should be those better characterizing the device, and used to judge the overall success of the study</p>	<p>Choice of endpoints, choice of endpoints:</p> <p>The guideline discriminates between endpoints for Phase II (exploratory, dose-finding) and Phase III (confirmatory) trials.</p> <p>In therapeutic exploratory trials, it is expected that the primary endpoint is, except for OAB, a urodynamic parameter that is appropriate for the condition to be studied. Signs and symptoms can be used as secondary endpoints.</p> <p>A single “objective” endpoint, such as the number of incontinence episodes, or two co-primary endpoints, e.g., number of incontinence episodes and QoL, are envisaged in the design strategies for confirmatory trials.</p> <p>The guideline also lists several endpoints that can be used for Phase II and Phase III studies, divided into PRO, qualitative and quantitative outcome measures</p>	<p>The main difference between the two guidelines emerges in the urodynamic endpoints.</p> <p>Within the FDA guidance, urodynamic measurements are listed among the possible endpoints of choice with the aim of “better characterizing the device for the success of study.” The EMA guideline clearly differentiates expectations of urodynamic measurement in Phase II as proof of concept and a clinical endpoint for confirmatory Phase III</p> <p>In Phase III, urodynamic measurements are also accepted to support clinical findings.</p> <p>Proposed endpoints as urodynamic, number of incontinence episodes, quality-of-life measurements, and generally quantitative and qualitative measurements are common to both documents.</p> <p>The FDA guidance emphasizes primary safety endpoints on the incidence and severity of adverse events, providing a list of those to be routinely</p>
STUDY DURATION	<p>Study duration:</p> <p>The study should be designed to assess whether the treatment effect persists for a clinically meaningful period. For UI devices that are intended either as a curative treatment or for long-term management, it is recommended to follow subjects during the premarket follow-up period for one year following treatment to document the stability of the treatment effect</p>	<p>Design, timing of assessment:</p> <p>The duration of Phase II studies should be long enough to include the time for reaching maximal effect: a study duration of six weeks is the minimum acceptable time for new classes of substances.</p> <p>To allow appropriate evaluation of efficacy of an investigational drug, a study duration of at least three months is expected.</p> <p>To provide an adequate safety database, additional follow-up is necessary so that the total study duration is at least 12 months; this may be performed as an open-label design if appropriate justification can be provided</p>	<p>Rather than differences, strong similarities can be appraised about minimal study duration, especially for the one-year safety follow-up required both for device investigations and drug trials, which are intended to address incontinence as a chronic condition.</p> <p>Of note in the EMA guideline is the specific reference about the intended use of drugs in older people, and the need to include a “sufficient” number of individuals over age 75, especially for safety reasons</p>

CRITERIA	FDA DEVICE UI GUIDANCE (2011)	EMA DRUG UI GUIDELINE (2013)	HIGHLIGHTS
<p>PATIENT SELECTION CRITERIA</p>	<p>Patient selection criteria:</p> <p>The protocol should clearly define the target population proposed for enrollment, including but not limited to, the following considerations:</p> <p>Category of incontinence</p> <p>Prior incontinence history (duration, severity and prior treatments)</p> <p>General medical history (comorbidities)</p> <p>Gender</p> <p>Age range</p> <p>Emphasis is given to the guidance about exclusion criteria and any confounding conditions that can affect study results.</p>	<p>Selection of patients:</p> <p>As it is difficult to separate prostate-related symptoms in men from incontinence not related to obstruction, it is preferred that men and women are investigated or analyzed separately. If separate studies are not performed for males and females, the study should be stratified for gender. Both gender subgroups should be analyzed separately.</p> <p>It is recommended to primarily include patients with “pure” stress or urge incontinence in studies of stress or urge incontinence. For practical reasons, it is often necessary to include patients with mixed incontinence in both kinds of studies</p> <p>Disease severity should be clearly defined using validated grading systems and sponsors should ensure that the target population is adequately reflected in the study population</p> <p>Older patients, specified as ages 65-74, 75-84, and more than 85 years of age, should be included in Phase III studies in sufficient numbers to permit evaluation of efficacy and safety in the older population, stratified by age group</p>	<p>Selection criteria categorized and listed in the FDA guidance are the same key criteria listed in the EMA guideline, with special considerations about gender.</p> <p>For device, investigations, specifically designed either for male or females could be required for intrinsic device characteristics caused by anatomical differences between genders.</p> <p>In drug studies, one requirement is also driven by disease considerations, as OAB, frequently associated with benign prostatic hyperplasia</p>

CRITERIA	FDA DEVICE UI GUIDANCE (2011)	EMA DRUG UI GUIDELINE (2013)	HIGHLIGHTS
OTHER(S)	<p>Operational implications are included, such as:</p> <p>Criteria for selection of investigational sites</p> <p>Statistical recommendation</p> <p>Risk analysis</p> <p>Study monitoring</p> <p>Case report form</p>	<p>Final sections of the EMA guideline do not address operational implications, but are related to considerations about:</p> <p>Tissue-engineered products (TEP) as emerging alternative for the treatment of SUI</p> <p>UI in children</p>	<p>Even under slightly different titles the FDA and EMA documents keep a similar structure aimed at identifying the key criteria for the appropriate design of studies, duration, endpoints and target population.</p> <p>Differences are more evident in the last sections, in which the FDA guidance maintains a more practical approach to the operational (clinical research) implications of device trials, while the EMA guideline explores and set requirements for new relevant areas of UI research as engineered products and pediatric trials</p>
PLACEBO AND BEHAVIORAL COMPONENTS	<p>There is a strong behavioral component to UI, and enrollment in a clinical may make subjects more aware of their voiding habits and potential risk factors. This phenomenon makes UI studies susceptible to a significant placebo effect.</p>	<p>There is a strong behavioral component to UI, and enrollment in a clinical study may make subjects more aware of their voiding habits and of potential risk factors, making UI studies susceptible to a significant placebo effect. The absence of a placebo control arm even in actively controlled trials for UI would require very sound justification and should be discussed with the regulatory authority in advance</p>	<p>There is a match in the wording used by both documents, remarking that investigations or studies with placebo comparison are needed to test efficacy and effectiveness of drug and devices, but medical device and drug companies are also warned about the high placebo effect expected in UI trials for the behavioral component of subjects and several other factors</p>

Even if the FDA guidance and the EMA guideline show differences related to intrinsic characteristics in clinical development of devices and drugs, the following common requirements are:

- Study design should be randomized, blinded and a controlled study. Blinding and placebo-controlled studies may pose additional operational issues for device investigations
- Early feasibility (device) and proof of concept (drug) studies are needed to elucidate the mechanism of action and to better define the target population for larger pivotal/ Phase III trials
- Target populations should be clearly identified, discriminating among the different type of UI, according to the mechanism of action for the device/ drug. Special considerations are applicable for gender and age criteria, related to anatomical (devices) and disease (drugs) characteristics, or safety concerns
- Duration of studies should be long enough to show efficacy and effectiveness and safety of drug/device. Minimal treatment duration is required for drugs, and one-year safety follow is recommended for both device and drug studies
- Meaningful endpoints should be selected to show efficacy, effectiveness and safety of the device/drug. While the choice of the most appropriate clinical endpoints, including urodynamic, clinical and PROs. The endpoints depend on the type of device for device investigations; for drugs, urodynamic are required in Phase I-II trials; clinical outcome and PROs are required in Phase III, which may include also urodynamic measurement in support of clinical efficacy
- A significant placebo effect is recognized and expected in UI trials and is caused by a strong behavioral component. Placebo comparison with a control arm is the preferred choice to show clinical efficacy/effectiveness

CONCLUSION

Although not a life-threatening condition, UI is a distressing and disabling condition which causes significant physical and psychological morbidity in individuals of all ages. Sufferers give up many aspects of their usual life with obvious detriment to their social interactions, interpersonal and sexual relationships, careers and emotional well-being.

UI continues to be a compelling and promising area in clinical development to address the unmet needs in women and the aging population. Research within the next decade is well-positioned to successfully develop new treatments beyond pharmacologic treatment — that are not only effective but, also have minimal side effects and risks. These include:

- Anti-cholinergics and beta-3 agonists
- Supportive self-care products, such as pads and adult diapers
- Invasive treatment or surgical procedures
- Bulking agents, slings or meshes

Regulatory framework is in place in the U.S. and Europe through guidance from the FDA and EMA to address the challenges in incontinence around protocol design, study endpoints, PROs and other parameters for studies across the spectrum of incontinence treatments.

As a global, full-service product development organization, PPD is well-positioned with medical, clinical development and operational expertise to understand intricacies of this therapeutic area and support successful clinical development in UI indications.

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