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## FROM THE ANALYST'S COUCH

# Female sexual dysfunction

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The success of the erectile dysfunction market ushered in a new era of opportunity for the pharmaceutical industry, one in which major companies have begun to devote time and resources to conditions that were previously considered part of the natural course of life<sup>1</sup>. Following in the footsteps of Pfizer, big pharma has used a vast amount of direct-to-consumer (DTC) and 'free-TC' advertising to create a US\$3-billion-plus market that has merged the strategies of mass consumer marketing with a traditional pharma sell.

The development of products to alleviate female sexual dysfunction (FSD) has lagged considerably behind that for male sexual dysfunction. Population-based studies published during the past decade have confirmed the far-reaching extent of FSD, but fears about the mixed aetiology of the disease, including psychological as well as physiological components, might have delayed pharma's interest. Moreover, the endpoint for FSD trials, usually measured as an increase in the number of satisfying sexual encounters, is much less tangible than the male equivalent: erections that can be measured in the clinic by a device such as the RigiScan.

The recent high-profile rejection of Procter and Gamble's (P&G) testosterone patch, Intrinsa, by the FDA advisory panel might indicate the setting of a new bar for lifestyle drugs. P&G will, at a minimum, have to submit safety and efficacy data from ongoing and recently completed Phase III trials in naturally menopausal women, and might have to conduct additional trials to confirm the long-term safety of testosterone administration in women. This mandate represents an enormous barrier to entry, putting the further development of testosterone-based therapies at significant risk and expanding the opportunity for novel mechanisms of action.

### FSD – the next big thing?

With more than 50 million potential sufferers in the United States, FSD could offer a larger market than male sexual dysfunction. Up to 63% of sexually active women might be affected by FSD, according to the National Health and Social Life Survey of nearly 2,000 women between the ages of 18 and 59 (REF. 2). FSD is an umbrella term for at least four separate disorders. Many women suffer from more than

one disorder, with associated impact on their personal relationships as well as self-esteem.

To address the multi-faceted symptomology of FSD, several routes of pharmacotherapy are probably needed. Off-label treatment of FSD currently includes hormone-replacement therapies, such as Solvay's androgen/oestrogen combination EstraTest, and phosphodiesterase 5 (PDE5) inhibitors such as sildenafil citrate (Viagra; Pfizer). Several drug-development strategies have focused on the 20 million post-menopausal women in the US, in whom well-documented hormonal changes are highly correlated with the onset of FSD.

### Emerging agents

P&G, partnered with Watson Pharmaceuticals, has been leading the way for FSD drug development. Their twice-weekly testosterone patch, Intrinsa, offers a novel application of the age-old knowledge that low levels of testosterone can lead to decreased libido in both men and women. In two pivotal Phase III trials, Intrinsa demonstrated statistically significant efficacy, increasing the number of satisfying sexual encounters by 51–74% in surgically menopausal women suffering from hypoactive sexual desire disorder. However, in absolute terms, this increase represents only about one additional sexual event per month, and though the panel agreed that this was clinically meaningful by a 14-to-3 vote, some questioned the clinical relevance. The lack of long-term safety data in women using testosterone with a required oestrogen supplement raised red flags, and the FDA experts expressed concern that off-label usage in pre-menopausal women would expose these women to significant risks beyond those seen in the post-menopausal trials. In light of the Women's Health Initiative study findings, which indicated an increased risk of cardiovascular events and breast cancer in patients on long-term hormone-replacement therapy, the current safety data were not deemed acceptable.

Other companies with new testosterone applications, including non-localized gel formulations by BioSante and Cellegy, are considering their options in the wake of the FDA decree. Decisions on whether to continue development of both Intrinsa and other formulations will ultimately be based on a risk/benefit analysis of potential return weighed against the expenses of the required trials. The void left in the wake of

the Intrinsa ruling creates a market primed for other novel mechanisms of action. Stemming from the knowledge that the clitoris and the penis originate from the same stem cells in development, some clinicians hoped to capitalize on the ability of PDE5 inhibitors to increase blood flow as a therapeutic in FSD. Both sildenafil citrate and tadalafil (Cialis, Lilly/ICOS) were under investigation for female sexual arousal disorder, but their trials have been halted due to lack of efficacy compared with placebo. Interestingly, although sildenafil citrate failed in its primary endpoint, it showed a positive effect on rates of orgasm.

Other novel agents, including alprostadil, tibolone and apomorphine, are also being studied, but are further off on the horizon for FSD treatment. Trials for these drugs are likely to continue as planned, but given their early stage of development, they harbour significantly more technical and clinical risk than established hormonal therapies.

### Market forecast

Market development, as with erectile dysfunction, will be contingent on the ability of pharmaceutical companies to harness the psychology of the mass market consumers. The recent proliferation of press coverage preceding the advisory committee review of Intrinsa closely resembles the pre-launch of sildenafil citrate, and has led to soaring rates of awareness among potential sufferers. In our forecast, awareness, coupled with an effort to seek help, are the two most sensitive correlates with market value. However, in the case of FSD, unlike erectile dysfunction, some of this awareness might be negative due to the safety concerns.

The potential size of the FSD market means that discovery efforts are unlikely to cease, regardless of the fate of Intrinsa and the testosterone therapies. The FSD market value could exceed US\$4 billion in the US alone with only 15% of patients captured on therapy. But many hurdles could prevent the realization of this market value. The mixed aetiology of disease could limit the uptake of drugs into niche segments. Moreover, an indication that limits therapy to post-menopausal women will weed out 75% of the sexually active population. Lastly, chronic therapies that must be used daily are less attractive options than PRN (as-needed) treatments such as sildenafil citrate, which could deter some users. ▶

# FEMALE SEXUAL DYSFUNCTION | MARKET INDICATORS

► FSD could be the next boon for pharma companies that are successfully able to integrate consumer mass marketing strategies with a more traditional pharma sell (see TABLE 1 for FSD subtypes). With more than 50 million women in the US suffering from FSD (FIG. 1), the potential market size could rival that of erectile dysfunction (FIG. 2), but significant technical and clinical risks exist. To achieve Viagra-like levels of sales, emerging agents must have broad labels, which is less likely for testosterone-based therapies. At maturity, the FSD market is more likely to be a conglomeration of mid-sized drugs, each of which address different symptoms of the complex disorder (TABLE 2).

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1. Moynihan, R. The making of a disease: female sexual dysfunction. *BMJ* **326**, 45–47 (2003)
2. Laumann, E. O. *et al.* Sexual dysfunction in the United States. *JAMA* **281**, 537–544 (1999)

**Online links**

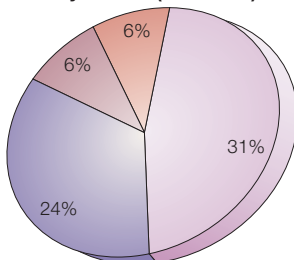
**FURTHER INFORMATION**

**Medline:**  
<http://www.nlm.nih.gov/medlineplus/femalesexualdysfunction.html>  
**MedScope:**  
<http://search.medscape.com/px/mscsearch?searchfor=Clinical&QueryText=female+sexual+dysfunction>  
**National Health and Social Life Survey:**  
<http://www.socio.com/srch/summary/aids/aid12-13.htm>  
**Access to this interactive links box is free online.**

Table 1 | **Female sexual dysfunction subtype**

Subtype	Epidemiology	Symptoms
Hypoactive sexual desire disorder	31%	Persistent loss of libido
Female sexual arousal disorder	22%	Libido is present but genitals fail to respond to sexual stimulation — for example, lack of lubrication and vaginal engorgement
Anorgasmia	6%	Delay or lack of orgasm after normal female arousal
Sexual pain disorder	6%	Defined by pain associated with intercourse, as a result of the involuntary contraction of vaginal muscles, which makes penetration difficult

**a 50–59-year olds (3.7 million)**



**b 18–59-year olds (53 million)**

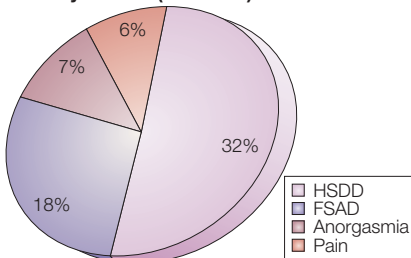


Figure 1 | **Prevalence of female sexual dysfunction (US).** From National Health and Social Life Survey 1992. FSAD, female sexual arousal disorder; HSDD, hypoactive sexual desire disorder.

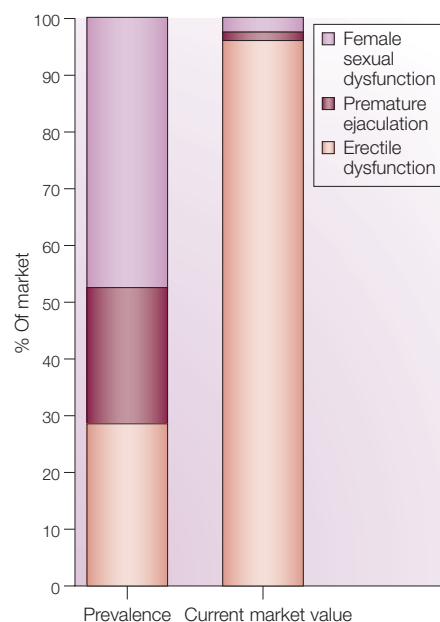


Figure 2 | **Relative size of sexual dysfunction markets.** Source: Trinity Partners, LLC estimates.

Table 2 | **FSD drugs in development**

Class	Product	FSD subtype	Company	Phase	Notes
Androgens (testosterone)	Intrinsa	HSDD	P&G, Watson	III	Twice-weekly patch
	LibiGel	HSDD	BioSante	II	Non-localized gel
	Tostrelle	HSDD	Cellergy	II	Non-localized gel
	Testosterone IVR	HSDD	Galen	II	Intra-vaginal; testosterone ring
	Testosterone MDTs	HSDD	VIVUS/Acrux	II	Non-localized topical spray
Oestrogen/androgen	EstraTest	HSDD	Solvay	Launched/III for FSD	
STEAR	Tibolene	HSDD/FSAD	Organon	Launched in Europe	
Vasoactive agents	Femprox (alprostadil)	FSAD	NexMed	II/III	Topical, in pre-menopausal women
	Alista (alprostadil)	FSAD	VIVUS	III	Topical, in pre-menopausal women
	Viagra	FSAD	Pfizer	II/discontinued	
	Cialis	FSAD	Lilly ICOS	II/discontinued	
	Vasofem	FSAD	Zonagen	II/on hold	
Centrally acting agents	VML 670	Drug-induced FSD	Lilly	II/on hold	Serotonin receptor agonist
	Flibanserin		Boehringer Ingelheim	II	
	Apomorphine	FSAD	Nastech	II	Dopamine agonist
	Wellbutrin	HSDD	GlaxoSmithKline		Women w/o testosterone deficiency
	PT-141	FSAD	Palatin	II	Melanocortin receptor agonist
NMI 870		Nitromed	II		

FSD, female sexual dysfunction; FSAD, female sexual arousal disorder; HSDD, hypoactive sexual desire disorder; STEAR, selective tissue oestrogenic activity regulator.