Pre-licensure Safety Data:

GARDASIL

[Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant]

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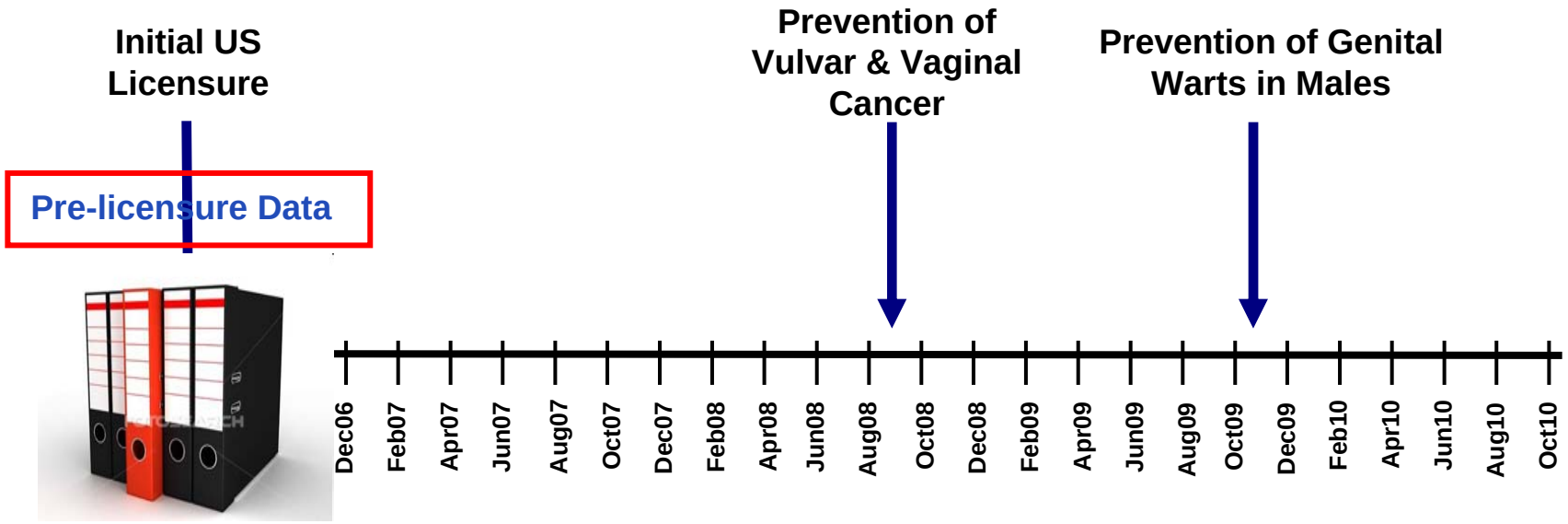
Background

- Each 0.5 mL dose contains
  - 20 mcg HPV 6 L1 virus-like particles (VLP)
  - 40 mcg HPV 11 L1 VLP
  - 40 mcg HPV 16 L1 VLP
  - 20 mcg HPV 18 L1 VLP
  - Adjuvant: 225 mcg amorphous aluminum hydroxyphosphate sulfate (AAHS)
- Administered 0, 2, 6 months IM
- Approved June 2006 for use in females 9 to 26 years of age for the prevention the following diseases caused by HPV 6/11/16/18:
  - cervical cancer
  - cervical, vulvar and vaginal dysplasia
  - genital warts

Major Licensing Actions and Material Reviewed



Pre-licensure Database

- **Pooled safety population**:
  - 12 randomized, controlled studies involving ~21,500 subjects 9 to 26 years of age
  - **~13,000** Gardasil recipients

- **Studies that enrolled pediatric subjects:**
  - Study 016: 3055 subjects 10 to 24 years of age
  - Study 018: 1796 subjects 9 to 15 years of age
  - **3430** Gardasil recipients (9 to 17 years of age)

Surveillance Methods for Safety Evaluation

- Safety Assessments were done at each vaccination visit and every 3 months post-vaccination series

- All subjects in the Detailed Safety Population were given a Vaccine Report Card (VRC) to record:
  - Oral temperature out to 5 days
  - Injection-site AE's out to 14 days
  - Systemic AE's out to 14 days

Overview of Safety, Days 1-15 Following Any Vaccination, Detailed Safety Population (9 to 26 Years of Age)

	Gardasil (N=6160)		**control** (N=4064)	
	n	(%)	n	(%)
With one or more AEs	5455	(90)	3416	(86)
Injection-site AEs	5035	(**83**)	2932	(**73**)
Systemic AEs	3591	(**59**)	2414	(**60**)
With vaccine-related AEs*	5243	(86)	3185	(80)
Vaccine-related injection-site AEs	5035	(83)	2931	(73)
Vaccine-related systemic AEs	2144	(35)	1460	(37)
With SAEs	37	(**0.6**)	26	(**0.7**)
Who died**	**1**	0	**1**	0

Source: Original Application - 2.7.4 Summary of Clinical Safety; VERSION 39.4; 17-Nov-2005, p.86
N = number of subjects in the respective vaccination group who had follow-up data
n = number of cases
*Causality determined by clinical investigator
**Deaths - Gardasil: 1 motor vehicle accident; Control: 1 motor vehicle accident

Deaths in the Pre-Licensure Trials, Entire Study Period, 9 to 26 Years of Age

	Gardasil* (N=11778)	**control** (N=9686)
Traumatic injury	3	2
DVT/PE	1	1
Pancreatic cancer (578 days post-dose #3)	1	
Drug overdose (4 days post-dose #3)	1	
Cardiac arrhythmia (27 days post-dose #2)	1**	
Sepsis, DIC (359 days post-dose #3)	1	
Respiratory failure, post C-section		1
Suicide		2**
Total	**8** (0.07%)	**6** (0.06%)

Source: Original Application - 2.7.4 Summary of Clinical Safety; VERSION 39.4; 17-Nov-2005, p.100-105

*Causality in each case (as determined by investigator) was either probably or definitely not associated with vaccine.

**Subjects <18 years of age.

Study 018 – Adolescent Immunogenicity and Safety Study

- Randomized, double-blind placebo-controlled, multicenter safety and immunogenicity study
- 9 to 15 year old subjects randomized 2:1 to receive Gardasil or saline placebo

Enrolled	Gardasil	saline
Boys 9-12 years of age	339	173
Girls 9-12 years of age	374	188
Boys 13-15 years of age	227	112
Girls 13-15 years of age	244	124
Total	**1184**	**597**

- Enrollment stratified by: gender (male to female = 1:1) and by age (9-12yo to 13-15yo = 2:1)

Study 018 – Safety Outcomes and Conclusions

	Gardasil (N=1165)		saline (N=584)	
	n	(%)	n	(%)
With one or more AEs	963	(**83**)	392	(**67**)
Injection-site AEs	877	(**75**)	292	(**50**)
Systemic AEs	541	(**24**)	134	(**23**)
New onset medical events (entire vaccination period)	520	(**44**)	280	(**47**)

Source: Original Application - CSR_V501_018_P018V1-12-Aug-2005, p.140, 181
N = number of subjects in the respective vaccination group who had follow-up data
n = number of cases

- **No deaths occurred during the study**
- **Five SAEs occurred in the Gardasil group* - each was assessed as unlikely related to vaccination**
- **Injection site AEs were mostly mild to moderate; none of the SAEs were related to local reactogenicity**
- **Safety profile in adolescents was judged to be comparable to the safety profile in older subjects**

*SAEs included: dysfunctional uterine bleeding, non-injection site cellulitis, acute renal failure, appendicitis, and diabetes

Pregnancy Outcomes – Pooled Safety Population

	Gardasil (N=10,418)		control (N=9120)	
	n	(%)	n	(%)
Subjects with pregnancies	944	(9.1)	957	(10.5)
Number of pregnancies (with known outcome)	**802**		**817**	
Congenital anomalies (total)	11	(1.37)	11	(1.35)
EDCn* within 30 days of vaccination**	**5**		**0**	
Live births	469	(58.5)	475	(58.1)
Fetal loss	333	(41.5)	342	(41.9)

Source: Original Application - 2.7.4 Summary of Clinical Safety; VERSION 39.4; 17-Nov-2005, p.170-179
*EDCn = estimated date of conception
**Diagnoses included hip dysplasia, pyloric stenosis, congenital hydronephrosis, left talipes equinovarus, and congenital megacolon.

- **After extensive review and discussion of the data, CBER reviewers, VRBPAC panelists, and a group of independent teratologists came to the conclusion that the evidence did not support a safety signal with regard to congenital anomalies, because, among other things, the widely divergent pathology among the cases did not suggest a pattern or syndrome, and vaccine exposure was temporally remote from the gestational critical period in each case.**

Conclusions

- No safety signal was identified in the data submitted in support of licensure
  - This was the conclusion of the review of both the overall dataset and the data in adolescents

- Continued safety evaluation in a larger population, through post-marketing studies and other pharmacovigilance activities, was recommended (and is being conducted)

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