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Quick Pulse

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MERCK'S INFANT DIARRHEA AND SHINGLES VACCINES GET FDA ADVISORY COMMITTEE RECOMMENDATION

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Merck is pinning much of its future on vaccines, and an FDA panel recently moved two of the company's vaccines – RotaTeq for infant gastroenteritis and Zostavax for shingles prevention – a step closer to market. On December 14, 2005, the Vaccines and Related Biological Products Advisory Committee unanimously recommended approval of RotaTeq, and the next day the same panel voted that Zostavax is safe and effective, but for a more limited age range than Merck had sought.

The panel first voted that Zostavax was neither safe nor effective for the proposed age group (over age 50), but at the last minute, the FDA proposed an additional question: Is it safe and effective in people age 60 or older? Yes, the panel said, but members recommended a long list of additional post-licensure studies.

ROTATEQ: Unanimous recommendation for approval

Rotavirus is the leading cause of severe diarrhea in infants and young children. A high proportion (~80%-90%) of children also experience vomiting and significant dehydration. In the U.S., rotavirus infection is responsible for 50,000-70,000 hospitalizations (4% of all pediatric hospitalizations) and 20-70 deaths annually. Most children are infected with rotavirus within the first few years of life regardless of socioeconomic status or environmental conditions. The highest incidence of rotavirus gastroenteritis is usually from 6-24 months of age.

Worldwide, each year rotavirus causes approximately 111 million episodes of gastroenteritis requiring home care, 25 million clinic visits, two million hospitalizations, and 352,000-592,000 deaths in children under age 5. By age 5:

- Nearly every child will have an episode of rotavirus gastroenteritis.
- 1 in 5 will visit a clinic.
- 1 in 65 will be hospitalized.
- ~1 in 293 will die, with children in the poorest countries accounting for 82% of rotavirus deaths.

There currently are no approved vaccines for rotavirus gastroenteritis. An earlier rotavirus vaccine, Wyeth's RotaShield (a live, oral, tetravalent vaccine, also with a three-dose schedule), was withdrawn from the market in July 1999, following 15 reports of intussusception in vaccinated infants. Intussusception was listed in the package insert as an adverse event that occurred in the pre-licensure trials. During the nine months that RotaShield was in use, ~1.2 million doses were given to

~600,000 infants. In October l999, preliminary estimates suggested that a fully implemented program of RotaShield use would have resulted in up to 1,600 excess intussusception cases, an excess risk of 1:2,500 vaccine recipients.

Background

On April 5, 2005, Merck filed a Biologics License Application (BLA) for RotaTeq, a live, oral, pentavalent vaccine for the prevention of rotavirus gastroenteritis in infants and children. The vaccine is a liquid formulation stored at 2-8 degrees Celsius (36-46° F). It contains five live, human-bovine reassortant rotaviruses. It is intended to be given in three doses, with the first dose given to healthy infants at 6-10 weeks of age, followed by two additional doses given 4-10 weeks apart.

Merck's proposed indication is "for the prevention of rotavirus gastroenteritis in infants and children caused by the serotypes G1, G2, G3, G4, and G-serotypes that contain P1 (e.g., G9). RotaTeq may be administered as early as six weeks of age."

GlaxoSmithKline reportedly is working on a rotavirus vaccine, Rotarix, and expects a European launch in 2006.

FDA perspective

FDA reviewers concluded that RotaTeq is efficacious, and they found no increased risk of intussusception. They noted that safety data from the Phase III trials demonstrated that the risk for intussusception was no higher with RotaTeq than placebo at 42 and 60 days post-vaccination, and they found no evidence of a clustering of intussusception cases within a 7-day or 14-day window post-vaccination. The REST trial met the primary safety endpoint with respect to intussusception. But the reviewers were unable to confirm a lack of interference of immune responses when RotaTeq is co-administered with childhood pertussis and diphtheria/tetanus vaccines, and they said the clinical data were not sufficient to support administration of a first RotaTeq dose in infants younger than 6 weeks or older than ~34 weeks.

FDA reviewers also noted that the vaccine was only administered to healthy infants and concomitant administration of live, oral poliovirus vaccine was not permitted. The vaccine was not studied in infants with:

- Underlying gastrointestinal disease.
- A history of immunodeficiency or HIV.
- Older than 12 weeks for the first dose or older than ~34 weeks for the third dose.
- A different administration schedule.

Merck Perspective

Merck officials, led by Dr. Penny Heaton, Director of the Department of Biologics Clinical Research at Merck Research Laboratories, did a very good job of presenting the data on

Intussusception with RotaTeq in Study 006 (REST)

Measurement	RotaTeq	Placebo	Relative risk
Intussusception at 42 days	6 cases	5 cases	1.2
Intussusception requiring surgical reduction	5 cases	5 cases	---
Intussusception deaths	1	0	---

Side Effects in Phase III Trials

Measurement	RotaTeq	Placebo
Diarrhea	24%	21%
Vomiting	15%	14%
Nasopharyngitis	7.0%	6.0%
Otitis media	15.0%	13.0%
Bronchospasm	1.1%	0.7%
Deaths	25 patients	27 patients

Efficacy of RotaTeq in REST and Study 007

Measurement	RotaTeq n=3,484	Placebo n=3,499	Vaccine efficacy
Any gastroenteritis	97 cases	369 cases	74%
Severe gastroenteritis	1 case	57 cases	57%
Vaccine efficacy estimates			
	FDA	**Merck**	
REST trial	73.9%	74.0%	---
Study 007	71.9%	72.5%	---

Efficacy of RotaTeq *(by ITT)* in All Phase II Trials

Measurement	RotaTeq	Placebo	Vaccine efficacy
Hospitalizations	10 cases	187 cases	94.7%
Any gastroenteritis	177 cases	435 cases	59.7%

Efficacy of RotaTeq by Season in REST Trial

Measurement	Vaccine efficacy
First season	
Any gastroenteritis	74%
Severe gastroenteritis	98%
Second season	
Any gastroenteritis	63%
Severe gastroenteritis	88%
Other results	
Reduction in hospitalizations	96%
Reduction in ER visits	93%
Reduction in physician office visits	86%

RotaTeq. Although the FDA and Merck did not always agree on the exact numbers, the differences were generally minor, and no one appeared to consider them a stumbling block to approval.

Because of the intussusception with RotaShield, Merck studied >70,000 infants in its pivotal Phase III trials – Study 006 (REST), Study 007 (an end-expiry dose trial), and Study 009 (a lot-consistency trial). Five Phase I and Phase II trials also were submitted to the FDA in support of the BLA.

Advisory Committee discussion

The panel had a number of questions, including:

- **Shed virus.** In a few children, RotaTeq virus was found in the child's stool, but Merck officials had no explanation for this. Dr. Heaton said, "It's a puzzle as to why children had vaccine strains in their stool."
- **Hemochezia (rectal bleeding).** Merck reported 11 cases overall, 4 with the vaccine and 7 with placebo.
- **Interaction with other childhood vaccines.**
- **Efficacy with fewer than the full three doses.** Dr. Heaton said, "There is some benefit from Doses 1 and 2, but clearly 3 is best."
- **Risk of intussusception.** A panel member wanted to know how the RotaTeq results differ from RotaShield, and Dr. Heaton responded, "REST was not a head-to-head study with RotaShield…We had a stopping boundary…If we had seen (a similar problem), we would have stopped the study early…There was also a difference in the pattern of cases…With RotaShield the highest risk was in the first two weeks after Dose 1…We saw no cases then …and no time clustering after a dose…We estimated there would be 6-12 cases in the first two weeks if the risk was similar to RotaShield, and we saw zero cases (in that time period)."

  Merck officials also assured the committee that no link to intussusception and age or dose was seen. There was no intussusception in premature infants who were vaccinated.

  It is unlikely that any intussusception cases were missed, a Merck official insisted, explaining, "Spontaneous reduction is uncommon. If there isn't medical attention, the outcome is grave, so I think we would pick them up anyway."
- **Post-licensure studies.** Merck officials said the company planned a large, prospective, HMO-based study of ~28,000 infants, looking at signal detection and safety 30 days after each dose, "We want to do it this way because in an HMO we can link the vaccine to clinical outcomes like intussusception…through electronic scanning of records. That allows rapid detection of intussusception or any safety signal. Rather than the usual annual reporting, this will assess safety in essentially real time… All cases of intussusception will be adjudicated by an independent panel." Merck also is doing a "rather large" study in babies born to HIV-positive mothers and looking at safety in children who are HIV-infected vs. not HIV-infected.
- **OUS efforts.** A Merck official said, "Last week we publicly announced that we are working…to do studies in the developing world…We plan to start trials in Asia and Africa next year." Trials in patients getting concomitant oral polio vaccine are ongoing now in Mexico, Guatemala, and Brazil.
- **Seizures.** Dr. Heaton said there were 41 cases of convulsions including febrile and epileptic convulsions: 25 (0.07%) with vaccine vs. 16 (0.05%) with placebo, with a similar incidence after each dose.
- **Durability of efficacy.**

FDA questions

The panel started with Question 3 first, and then proceeded to the key efficacy and safety questions.

QUESTION 3: ***Discussion only (no vote).*** *Please identify any other issues that should be addressed, including post-licensure studies, in particular:*

- *Intussusception.*
- *Pharmacovigilance plan.*
- *Use with routine vaccines in immunocompromised children or children taking steroids or other chronic immunosuppressive therapies or other special populations.*

The committee agreed all of these need to be studied – plus seizures.

The panel chair commented, "It seems clear to me that the sponsor presentation clearly raised questions on concomitant use with other vaccines…Both the effect on serologic and perhaps on the efficacy of other vaccines really needs to be explored further, especially with regard to DTaP (the diptheria-tetanus-pertussis vaccine). That needs to be done in follow-up…With the very expanding list of vaccine options for pediatrics, this may be vaccine specific and needs to be looked at. Schedules vary tremendously in pediatric offices, and that needs to be addressed. Also there should be plans to address the use with the oral polio vaccine and in HIV, etc., children."

QUESTION 1: *Are the available data adequate to support the efficacy of RotaTeq in prevention of rotavirus gastroenteritis caused by serotypes G1-4 that contain P1 (e.g., G9) when the first dose is administered at 6-12 weeks of age, followed by 2 subsequent doses separated by 4-10 week intervals? If not, what additional information should be provided?*

Yes, unanimously.

Panel member comments during the vote included:

- "This is pretty easy…The vaccine looks highly effective, and there were no holes in the presentation on efficacy. Yes, it satisfies the criteria."
- "I am satisfied it is effective, and they have proved that."
- "I commend the sponsor on a very coherent and comprehensive program…I won't say it was a joy to work with you, but it was a pleasure."

QUESTION 2: *Are the available data adequate to support the safety of RotaTeq in the prevention of rotavirus gastroenteritis in a three dose series, with the first dose at 6-12 weeks, followed by two additional doses?*

Yes, unanimously but with some reservations.

Panel member comments during the vote included:

- "Yes, but there are a few safety issues…It is possible there are some excess cases of intussusception…My back of the envelope calculation is that…the net effect on hospitalizations is still around 80%, down from 95%, but still very substantial. In trying to grapple with balance of risk and benefit, it seems to be clearly in favor of the vaccine."
- "Yes, the available data are adequate…but there are important issues to be addressed post-licensure, including intussusception after each dose, and stratifying by age at each dose."
- "Yes, but I'm left feeling a little bit uncertain. There was no clustering of intussusception…but I'm concerned about the age when children will be immunized…There is a relatively broad window around each dose, so you can wind up with some children who are quite old when they get the final dose…Implementation will be quite a challenge, and it will fall to our ACIP (the CDC's Advisory Committee on Immunization Practices) colleagues…The data driven part of my brain says, yes, safety looks good, but my gut says I wish there were other data…We cannot afford another problem with a replication attenuated vaccine for rotavirus."
- "I agree the data support the safety of the vaccine, but I do feel some uneasiness on the potential for occurrence of intussusception in the post-licensure period and support data collection that will be done as well as development of a comprehensive way to look at seizures."
- "If this were a highly lethal disease with serious long-term morbidity in the U.S., we would not be requiring a trial with 72,000 children enrolled…That is part of the struggle here…But, within the parameters of this study, safety has been shown."
- "It will be important to have surveillance on serotypes, but, yes, the data are convincing."
- *Chair:* "The data to me are very reassuring on intussusception. I don't know how you could do better without adding another 70,000 patients. We are a bit of a victim of your own (Merck's) success. There is so much data that a whole lot of things were uncovered, including this possible issue of seizures. I think the data very strongly support safety…Perhaps we all have to live with this back of the head, tentative feeling until we've lived with this vaccine for a while…but I vote yes."

ZOSTAVAX: Approval recommended only for age ≥60

Currently, there is no preventive treatment for herpes zoster (HZ), which is a reactivation of the varicella-zoster virus that causes chickenpox. Antivirals can reduce the severity of acute HZ and may shorten the duration of post-herpetic neuralgia (PHN), but they have limited effect on the incidence of PHN, and corticosteroids have no effect on either the incidence or severity of PHN.

About one million cases of HZ occur annually in the U.S., and ~21% of these are in people age 50-59, with 40% in people ≥age 60. The annual risk begins to increase markedly at around age 50, rising sharply thereafter. The lifetime risk of developing HZ is 30% or more, but about 50% of 85-year-olds will have had ≥1 episode of HZ. Ten percent of HZ patients develop PHN, and the risk of PHN also increases dramatically with age. PHN can persist for months to years.

Merck is seeking approval for Zostavax (varicella virus vaccine) – a single-dose, sterile, preservative-free, live attenuated vaccine – for: Immunization of adults ≥50 years for prevention of herpes zoster, post-herpetic neuralgia, and reduction of acute chronic zoster-associated pain.

The advisory committee voted unanimously that the vaccine was not shown to be effective for that indication, and panel members also voted it wasn't safe – in both cases because the proposed indication included people age 50-59. After the vote, the FDA added another question: Is Zostavax safe and effective for people age ≥60, and the panel voted unanimously yes, but they recommended additional post-licensure studies. Thus, it is likely Merck will only get approval for use in people age 60 or older.

Merck has a study ongoing of a new formulation.

The data

Efficacy data on a large number of patients were submitted from two studies:

- **Protocol-004** [also known as the Shingles Prevention Study (SPS)], a randomized, double-blind, placebo-controlled, 22-center study of the safety, efficacy, immunogenicity and consistency of three manufacturing lots of Zostavax in 38,546 relatively healthy adults ≥age 60 getting optimal care. This Department of Veterans Affairs (VA) study was conducted in collaboration with

the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) and Merck.

- **Protocol-009**, a three-year, controlled, double-blind, multicenter, trial in 698 patients ≥age 50, comparing a high potency dose of 207,000 pfu to a low potency dose of 58,000 pfu.

There were two-co-primary endpoints and three secondary endpoints in the SPS trial, but the FDA said Merck only had to meet one of the primary endpoints for the study to be a success.

FDA reviewers and panel members raised several issues and/or concerns with the Zostavax data, but the key issues boiled down to:

- Lack of data on people age 50-59.
- Insufficient data on people age ≥80.
- A waning effect of the vaccine as people age, when they need it most.

The issues

Among the issues raised by FDA reviewers and panel members were:

- **Clinical benefit.**
  - There was no statistically significant effect of the vaccine on the rates of mortality, hospitalizations (overall and zoster-related), serious morbidity, use of pain medications, and interference with activities of daily living (ADLI) over the course of the study. However, a panel member commented, "I'm surprised at how few hospitalizations are HZ-related…What this is saying is the vaccine didn't reduce any HZ hospitalizations, but they are so incredibly infrequent that it doesn't matter too much."
  - **Burden of illness (BOI).** There was minimal efficacy on BOI ***beyond*** the efficacy on the HZ incidence.
  - **Pain.** The clinical significance of the decrease in pain was unclear.

- **Durability of effect.** There was a trend of decreasing efficacy in all three major efficacy endpoints over the first three years post-vaccination. Panel members also wanted to know whether people immunized between age 50-59 would have protection later in life when they were at higher risk from HZ. A panel member asked, "If the vaccine is administered at age 50, will patients need a booster?" Another panel member said, "We may not be doing people a favor by shifting HZ from the 50s to the 60s or later with a vaccination since we don't know how long the vaccination lasts, and the risk of vaccination may be

Efficacy of Zostavax in Protocol-004

Measurement	Zostavax n=19,270	Placebo n=19,276	Vaccine efficacy
Completers	95.2%	95.2%	---
Cases of HZ by ITT	322	662	---
Cases of HZ by MITT	315	642	---
Primary endpoint #1: HZ burden of illness	8.6% (p=0.08)	12.5%	61.1%
Primary endpoint #2: Incidence of PHN occurring or persisting at Day 90	---	---	66.5%
Secondary endpoint #1: Incidence of HZ	20%-43%	4%-10%	51.3%
Secondary endpoint #2: Duration of clinically significant pain	20 days (p<.001 by MITT, p=.041 in evaluable HZ cases)	22 days	---
Secondary endpoint #3: Substantial interference with SIADL	36.2% (Nss)	39.4%	---
Median HZ BOI	82.50	87.75	0.25
Safety			
Vaccine-related adverse events	6.3%	4.9%	---
Injection site reactions (ISR)	48.3%*	16.6%	---
Serious adverse events	1.24%	1.38%	---
Serious vaccine-related adverse events	0.01%	0.01%	---
Systemic adverse events	24.7%	23.6%	---
Elevated temperature	0.8%	0.9%	---
Hospitalization rate per 1,000 patient years	107.4	107.3	---

* Mostly mild

Adverse Event Monitoring Substudy of Protocol-004

Adverse event	Zostavax age 60-69 n=1,732	Zostavax age ≥70 n=1,613	All Zostavax n=3,345	Placebo n=3,271
Any adverse event	64.95%	50.50%	---	---
Serious adverse events	1.27%	2.63%	1.92%	1.26%
Serious vaccine-related adverse events	0	0	0	0.03%
Died	0.06%	0.13%	0.09%	0.06%
ISR Day 0-42	---	---	48.3%	16.6%
Erythema	---	---	35.8% (p<.001)	7.0%
Pain/tenderness	---	---	34.5% (p<.001)	8.5%
Swelling	---	---	26.2% (p<.001)	4.5%

Efficacy and Safety with Zostavax in Protocol-009

Measurement	Higher potency n=461	Lower potency n=234
ISR age 50-59	82.9%	69.4%
ISR age ≥60	55.7%	56.4%
Systemic adverse events age 50-59	40.7%	45.2%

near the risk of HZ in a later decade." The panel chair said, "I think there are considerable issues on immunization in 50-59-year-olds, and it is clear there are not data that clearly support that…I think there are problems with the recommendation for that group." A Merck official said, "It is not known yet whether people will need a booster. The critical question is to take people out to 10 years and determine if there is any waning of effect at any point. We have not seen that yet, but it could happen. What could be explored is when or if a booster is needed…We hope the persistence study will answer that." At another point the same Merck official said, "From a clinical protection standpoint, a decline in durability has not yet been observed, and one would expect the durability of 50-59-year-olds would be at least as good as seen with other vaccines… We would anticipate, should the data evolve to show waning efficacy, that there would be benefits to a subsequent dose."

➢ **Follow-up.** A relatively small proportion of subjects with three-year follow-up, which was mostly through patient diaries and monthly telephone calls.

➢ **Lack of data on special populations.** Patients on inhaled corticosteroids, nursing home patients, cognitively impaired patients, etc., were all excluded from the trials. A Merck official responded, "Two sites recruited at nursing homes…And there were a handful of subjects who entered with cancer, and there were no safety signals there…In the future we will look to judiciously expand the population with further studies."

➢ **Efficacy by age.** With increasing age there was a consistent trend toward progressive loss of vaccine efficacy in prevention of HZ. A biostatistician on the panel said, "There is a suggestion there may be more benefit in prevention of HZ in >age 70. What we are seeing is strong evidence of an age effect on HZ…To the extent the BOI data are interpretable, is there any evidence, beyond preventing HZ, that more severe, prolonged cases are fewer? The answer is no, not at all in the age 50-69, but above age 70, maybe."

➢ **Titer levels.** Lower and less discriminatory titers at early time points (e.g., 2-3 weeks) were observed than might be expected since the vaccine is acting as a "booster" in subjects with previous primary varicella (chickenpox) infection.

➢ **Gender differences.** More injection site reactions in females (40%-50%) than in males (15%-25%).

➢ **Injection site reactions.** In Protocol-009, subjects at the higher dose experienced higher rates of solicited and non-solicited vaccine-related injection site reactions, although few were severe, but systemic vaccine-related adverse events were not increased at the higher dose. Injection site reactions also were higher in the 50-59 age group.

➢ **Lack of data on younger (<60) and very old patients (≥85).** Very few patients (<300) were studied in the 50-59 age group, and most of these were in the smaller safety study (Protocol-009). There were more patients over age 80 (~2,500), but few age ≥85.

Efficacy and Safety with Zostavax by Age

Measurement	Zostavax age 60-69	Zostavax age 70-79	Zostavax age ≥80	Zostavax overall	Placebo
Vaccine efficacy in preventing HZ	63.9%	37.6%	18.3%	---	--
HZ BOI	65.5%	59.1%	37.7%	---	--
PHN	65.6%	N/A	39.4%	---	--
ISR	~30%-43%	20%-30%		20%-43%	4%-10%

➢ **Actual dose.** Panel members wanted to know the actual dose of vaccine going into people in the clinic. Merck officials explained that this changes over time because it is a live virus, but the expiry potency (minimum potency) is 19,500.

➢ **Change in endpoints.**

- The co-primary endpoint in Protocol-004 was re-defined during the study to PHN at Day 90 post-HZ rash instead of Day 30 post-HZ rash. If the original definition was used, the trial would have failed this endpoint. The FDA noted, "Given that the majority of cases of PHN resolve completely within a few weeks after HZ rash onset, the use of a 90-day cutoff for evaluation of ***treatments*** for PHN appears useful. It is not clear that a 90-day cutoff is the most appropriate in a ***preventive*** study."
- Incidence of HZ, a tertiary endpoint, was changed, with FDA approval, to a secondary endpoint.

➢ **Difference in analysis.** The FDA and Merck statisticians adjudicated the data differently, and an FDA panel member suggested this had to do with "right-hand tail" and, to a lesser extent, to definitions. In the briefing documents, the FDA also said the completeness of the data was "unclear," but an FDA official told the panel, "We were recently advised the data are in a different form, in a different column, but we were just advised of this a few days ago."

FDA questions and Advisory Committee votes

QUESTION 1: *Are the available data adequate to support the efficacy of Zostavax when administered to individuals ≥50 years of age in:*

- *Preventing HZ?*
- *Preventing PHN?*
- *Preventing PHN beyond the effect on HZ?*
- *Decreasing sponsor-defined burden of illness (BOI)?*

If not, what additional information is needed?

No, unanimously.

Panel member comments included:

- *Dr. Ruth Karron, a pediatrician and infectious disease expert at Johns Hopkins School of Hygiene and Public Health:* "The vaccine has shown efficacy in age 60-69,

but the efficacy against the incidence of HZ is substantially decreased over age 80…While it is likely something effective over age 60 would be effective under age 60, that was not shown. The duration of effect, the need for booster doses, and the question of whether immunizing the young elderly will only delay time-to-occurrence potentially with worse complications are issues…So my conclusion is the data are not adequate in persons age >50, though it may be adequate in a subset of that group."

- *Thomas Fleming, PhD, a biostatistician with the University of Washington:* "Not only does this approval have to depend on age, but it certainly is problematic that there is an absence or limited information on critical cohorts (age 50-60, comorbidities, chronic immunosuppression, minorities, age >80, and certainly age >85)… There is at least uncertainty about the prudence of delaying HZ cases of people in their 50s when they are at low PHN risk…On the efficacy in patients over age 60, I believe there are positive efficacy data to establish the effects on HZ…Experience has shown it is treacherous to look at results by subgroup…but in this case, the evidence of a lesser effect in older participants is very strong…On the effect beyond the prevention of HZ…my own sense is it is age specific: In the 60s, there is no difference…In the 70s and even into the 80s, there is indication the effect (on PHN) is exceeding the effect on HZ…At this point, with BOI, like PHN, there is a suggestion of more than just an HZ effect in the 70s and 80s."
- *Dr. Bonnie Word, an Assistant Professor of Pediatrics at Baylor College of Medicine/Texas Children's Hospital:* "I'd vote yes if the age were 60, but if it is 50, then no…The indication the sponsor is seeking is age >50, but there are only data on age >60…We are asked for a judgment call or a leap of faith for younger people…but we need hard and fast data."
- *Unidentified panel member #1:* "I'm concerned about the 50-59 and over 80 categories. And I have serious concerns about the quality of pain data."
- *Unidentified panel member #2:* "It is difficult to answer the FDA questions because of a lack of data in the 50-59 age group. In the age over 60, there is a very definite effect which carries into 70s and perhaps 80s…An indication for PHN would encourage patients to vaccinate when they get HZ to prevent PHN…I'm already getting vaccination requests even though patients have had PHN for years…The labeling needs to be careful to keep from confusing patients (on preventing PHN beyond the effect on HZ)…There does appear to be an effect on BOI…The data suggest patients older than 70 did have less severe pain even when it persisted."
- *Dr. David Markovitz, Professor of Infectious Diseases at the University of Michigan Medical Center:* "No on age 50-59, yes on age ≥60…Obviously, there aren't any data to say it should be licensed for age 50-59. That is unfortunate. My guess is it will work when the company does the studies…I'm a little reluctant to endorse a bridging study…That being said, I like the data over age 60, certainly in preventing HZ. PHN and BOI are important for labeling, but clinically, if you can prevent HZ that is still an important improvement…In real life clinical efficacy in preventing HZ would be fine with me."
- *Chair, Dr. Gary Overturf, Professor of Pediatrics and Pathology at the University of New Mexico:* "My biggest concern is giving Zostavax to a large population (age 50-59) without adequate safety data…Another issue is the long-term public health consequences of the vaccine in that age group…I don't think there is enough information (to do that)…To me, the data do support the use of the vaccine in people over age 60 very clearly, and I think there is some suggestion it probably does lower severity in people over age 70. There is a relatively minimal effect (in that age group), but it could have a major public health consequence anyway, so I support use over age 60."

QUESTION 2: *Are the available data adequate to support the safety of Zostavax when administered to individuals age >50? If not, what additional information should be provided?*

The no votes outweighed the yes votes.

Panel member comments included:

- "Age 50-59 only had 185 patients. There were not enough patients for adequate safety data. Over age 60, the SPS trial was landmark…and adequate."
- "Safety is benefit:risk. Safety in 50s, like the efficacy data, is lacking. On 60s to 80s, it is unclear."
- *Chair:* "There are not enough data to support safety over age 50."

QUESTION 3: *Identify any other issues that should be addressed, including post-licensure studies. In particular, please address:*

a. *Comorbid conditions, e.g., nursing homes and assisted living facilities.*

b. *Use among persons taking chronic immunosuppressive therapies, including corticosteroids.*

c. *Use of the vaccine in certain subsets by age.*

d. *Duration of immunotherapy.*

e. *The pharmacovigilance plan.*

Panel members had already addressed most of these issues, but their additional comments included:

- *Dr. Monica Farley, an expert in bacterial infectious diseases at Emory University School of Medicine:* "Comorbid conditions are not a big concern. Use among

persons taking immunosuppressants will need careful attention in the pharmacovigilance studies – What will happen with people who had the varicella vaccine when they age?"

- *Unidentified panel member #1:* "Interaction studies with other vaccines are critical…There may be a potential for the vaccine strain to spread cutaneously in nursing homes."
- *Unidentified panel member #2:* "Nursing homes and assisted living facilities especially need to be studied. This is a group tailor-made for a preventive-type treatment like the vaccine…HIV is a ready model (for study in immunosuppressed people)."
- *Daniel Scharfstein ScD, a biostatistician at Johns Hopkins:* "There are not enough data on comorbid conditions or on people taking chronic immuno-suppressives…And I'm concerned about the generaliza-bility of the data. This was a predominantly white study."
- *Dr. Fleming:* "It is disappointing that there is limited evidence on minorities…But I congratulate the sponsor for a clinical endpoint trial, not just an immunogenicity study…And the sponsor showed over 3-4 years that there is durable efficacy."

QUESTION 4: *The chair was asked by the FDA to poll advisory committee members one more time – Is there efficacy and safety against HZ at age 60 and older?*

Yes, unanimously on both efficacy and safety.

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