



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

To:	The File
Date and Time:	October 10, 2012
Summary:	Mid-Cycle Meeting Summary
STN #:	125428/0
Supplement Type:	Original Application
Sponsor:	Dynavax Technologies Corporation
Product:	Hepatitis B Vaccine (Recombinant), Adjuvanted
Meeting Chair:	Marian Major Ph.D.
Meeting Recorder:	Richard Daemer, Ph.D. and Katherine Berkhausen, CAPT. USPHS
Signature:	

CBER/FDA Attendees

Review Assignment

Chair
Lead RPM
Co-RPM
Clinical (efficacy)
Clinical (safety)
Product (CMC)
Product (Adjuvant)
Toxicology (Preclinical)
Assays Stats
Statistical
Pharmacovigilance
Advertising/Promotional Labeling
BIMO
Facilities/DMPQ
Facilities/DMPQ
Product Quality
Product Quality
Product Quality
Product Quality
Lot Release
Carton/container

Committee Member

Marian Major
Richard Daemer
Katherine Berkhausen
Alexandra Worobec
Lori Smith
Iryna Zubkova
Brenda Baldwin
Claudia Wrzesinski
Martha Lee
Mridul Chowdhury
Manette Niu
Kristine Khuc
Bhanumathi Kannan
Destry Sillivan
Priscilla Pastrana
Muhammad Shahabuddin
Lokesh Bhattacharyya
Karen Campbell
James Kenney
Cheryl Hulme
Daphne Stewart

OTHER ATTENDEES:

Marion Gruber	OVRP, Director
Wellington Sun	DVRPA, Division Director
Loris McVittie	DVRPA, Deputy Division Director
Douglas Pratt	DVRPA, Policy
John Elterman	CBER, OCBQ
Dale Horne	CBER, OBE
Wei Hua	CBER, OBE
Andrea James	DVRPA
Lewis Schragar	DVRPA
Elizabeth Sutkowski	DVRPA
Rakesh Pandey	DVRPA
Tim Nelle	DVRPA
Carmen Collazo	DVRPA

1.0 PURPOSE

To discuss the milestones, review progress, outstanding issues related to the ongoing review of Hepatitis B Vaccine (Recombinant), Adjuvanted.

2.0 BACKGROUND

BLA 125428/0 (Sequence #534454) was submitted by Dynavax Technologies Corporation on April 26, 2012 and received by CBER on April 26, 2012.

The proposed indication is for immunization against infection caused by all known subtypes of Hepatitis B virus in adults 18-70 years of age.

HEPLISAV™ is a recombinant hepatitis B vaccine for active immunization against hepatitis B virus infection. The immunogenic component, hepatitis B surface antigen (HBsAg), subtype adw, is produced in the yeast strain *Hansenula polymorpha* using recombinant technology. The Drug Substance is formulated with 1018 ISS Adjuvant to produce HEPLISAV Drug Product, which is a sterile, liquid dosage form that is administered as an intramuscular injection. HEPLISAV Drug Product is formulated as 6000 mcg/mL 1018 ISS Adjuvant and 40 mcg/mL HBsAg Drug Substance in 8 mM sodium phosphate, 154 mM sodium chloride, 0.01% w/w polysorbate 80, pH 7.0 buffer.

The finished vial (0.7 mL) contains 4200 mcg of 1018 ISS Adjuvant and 28 mcg of HBsAg Drug Substance of which an administered dose of 0.5 mL contains 3000 mcg of 1018 ISS Adjuvant and 20 mcg of HBsAg Drug Substance.

The HEPLISAV regulatory background is summarized as follows:

- 30 Sep 2005, IND 12692 filed for evaluation of rHBsAg-1018 ISS in end stage renal failure patients.
- 27 March 2007, IND 13332 filed for evaluation of rHBsAg-1018 ISS in healthy adult subjects.

- 5 March 2008, initial serious adverse event report (SAE) of c-ANCA positive Wegener's Granulomatosis reported in a 55 year otherwise healthy German woman enrolled in the phase 3 study DV2-HBV-10 under IND 12692, Amendment 6. The event was deemed possibly associated with HEPLISAV and biologically plausible.
- 14 April 2008, INDs 12692 and 13332 were placed on clinical hold.
- 18 Sept 2008, Dynavax submitted a complete response to clinical hold. Review of the response indicated remaining safety concerns regarding risk of autoimmune disease, revised inclusion/exclusion criteria, and requirement for closer safety monitoring for autoimmune adverse events of interest. A continued clinical hold was issued on 17 October 2008 for both INDs.
- 08 Jan 2009, CBER Clinical Hold Oversight Meeting to discuss the SAE of Wegener's granulomatosis.
- 24 March 2009, complete response to clinical hold submitted by Dynavax.
- 24 April 2009, continued clinical hold recommended by the clinical reviewer.
- 09 Aug 2009, Dynavax submitted a complete response to clinical hold and provided a comprehensive prospective safety monitoring plan and algorithm to evaluate autoimmune adverse events.
- 26 August 2009, clinical hold was lifted for IND 12692.
- 25 Jan 2012 Pre-BLA Meeting with FDA to discuss filing of HEPLISAV for use in healthy adults.
- 26 April 2012 BLA filed for HEPLISAV with the FDA.
- Action due date: February 24, 2012.

2.1 Review Committee

As above.

2.2 Milestones

Milestones:

<u>Milestones:</u>	<u>Projected Date</u>
▪ Application Received	April 26, 2012
▪ Committee Assignment	May 8, 2012 (+2 days)
▪ 1st Committee Meeting	May 15, 2012 (+ 2 days)
▪ Filing Meeting	June 5, 2012 (+ 5 days)
▪ Filing Letter Issued	June 22, 2012 (+ 3 days)
▪ 1st draft reviews (by day 90)	July 25, 2012
▪ PMC/R Determination	September 23, 2012
▪ Lot Release /Testing Plan Draft	September 23, 2012
▪ Present to PeRC	October 3, 2012
▪ Mid-Cycle Review Meeting	October 10, 2012
▪ 2 nd draft reviews (by day 175)	October 26, 2012
▪ VRBPAC Date	November 15, 2012
▪ Final Reviews - Signed/Uploaded (T-60)	December 17, 2012
▪ OVRP Rep and SWG Notified	January 7, 2013
▪ Labeling Comments to Sponsor (T-30)	January 12, 2013
▪ Lot Release Clearance/Product Testing	January 22, 2013
▪ Notify Dynavax of PMC/PMR	January 25, 2012
▪ Labeling Complete	February 6, 2012
▪ First Action Due	February 24, 2013

2.3 Meetings [Completed meetings grayed out]

First Committee Meeting:	May 15, 2012
Filing Meeting:	June 5, 2012
Monthly Team Meetings:	June 19, 2012
	July 9, 2012
	July 16, 2012 (testing discussion)
	August 29, 2012
	Sep 4, 2012 (testing procedures)
	September 18, 2012
	November 5, 2012
	December 12, 2012
	January 9, 2013
PeRC:	October 3, 2012
Mid-Cycle Review Meeting:	October 10, 2012
VRBPAC:	November 15, 2012
SWG:	Not Scheduled
Labeling Meetings:	Not Scheduled

2.4 Information Requests

IR Request Number and Date	CBER Rep(s)	Request	CBER Requester for Info	BLA Amendment Response	BLA Amend. Received	Date Reviewed
#1 6/18/2012	Daemer, R	IR for statistical information; SOPPs	M. Chowdhury L. Bhattacharyya	125428.0.01	7/17/12	
#2 7/12/2012	Daemer, R.	Manufacturing Process and Controls	S. Kaur	125428.0.02	8/1/12	
#3 7/26/2012	Daemer, R.	QC Analytical Procedures Pharmacology	J. Kenney H. Qin	125428.0.03	8/9/12	
#4 8/1/2012	Daemer, R. Berkhousen, K	Revised 356h Establishment	Daemer Berkhousen	125428.0.05	9/13/12	
#5 8/6/2012	Daemer, R	Establishment: storage, manufacturing process, container closure systems	D. Sullivan P. Pastrana	125428.0.08	10/9/12	
#6 8/6/2012	Daemer, R.	Info on BIMO sites	B. Khannan	125428.0.04	8/17/12	
#7 8/16/2012	Berkhousen, K	LACBRP for QC testing	L. Bhattacharya M. Shahabiddin	125428.0.05 (Partial Response: Only comment 1 of 12 addressed)	9/13/12	

#8 8/16/2012	Berkhousen, K	Lot release templates, reagents, sampling, info on drug substance/product	J. Kenney I. Zubkova K. Campbell	125428.0.06 (Partial response)	9/21/12	
#9 9/12/2012	Berkhousen, K	Clinical safety data	L. Smith	125428.0.07	9/28/12	
#10 9/26/12	Daemer, R	Deletion of tests	L. Bhattacharyya B. Baldwin K. Campbell			
#11 10/5/12	Daemer, R.	Clinical safety and product	L. Smith I. Zubkova			

2.5 Amendments

STN /Date Received	Summary
125428/0.01 (July 17, 2012)	Response to 6/18/2012 IR. Revised data sets.
125428/0.02 (August 1, 2012)	Response to 7/12/2012 IR. Manufacturing process & control info.
125428/0.03 (August 9, 2012)	Response to 7/26/2012 IR. Answers to QC Analytical Procedures Pharmacology.
125428/0.04 (August 17, 2012)	Response to 8/6/2012 IR. Answers to BIMO for location of data from the closed site.
125428/0.05 (September 13, 2012)	Response to 8/1/2012 IR. Corrected 356H. Response to 8/16/2012 IR. Responded to LACBRP (SOPPs) request #1 only.
125428/0.06 (September 21, 2012)	Response to 8/16/12 IR. Responded to request for endotoxin specifications and acceptance criteria. Lot release protocol templates will be sent ASAP to the custodian.
125428/0.07 (September 28, 2012)	Response to 9/12/12 IR. Clinical safety data information.
125428.0.08 (October 9, 2012)	Response to 8/6/12 IR. Facilities information.

3.0 DISCUSSION TOPICS: STATUS AND ISSUES

3.1 Product:

CMC: The review has not revealed significant problems with the preparation, manufacturing process, specifications, and stability of the product.

- The Sponsor requested to remove several tests from the Stability testing program. After discussion with the reviewing committee it was decided that several but not all tests may be removed from the HBsAg Drug Substance Stability testing program,

including the (b) (4). This information will be conveyed to Dynavax.

Adjuvant: It was noted that the 3 lots of 1018 ISS adjuvant used in the pivotal lot consistency trial DV2-HBV-16 were manufactured under Process (b) (4). The lot used in the pivotal efficacy trial DV2-HBV-10 was under Process (b) (4).

Review is 100% complete until IR response is provided by Dynavax. IR includes 20 questions/comments that should be easy to provide a response, and 5 questions/comments that may take some time to provide a response.

3.2 **Facilities:**

- Response to DMPQ information request received by FDA October 9, 2012. DMPQ has not had the opportunity to review yet.
- Dynavax has stated they will respond completely to issues identified during the inspection by Nov 20, 2012. Dynavax should be informed that they should move this date up.
- Given the number and severity of the 483 observations, as well as potential issues with respect to DMPQ's information request, we believe that it will be difficult for Dynavax to respond completely to all issues identified to date within the remaining review clock. All issues presently identified can be solved, but solving them likely will require a substantive effort.
- There are a number of concerns related to the manufacturing process. The quality system the firm currently has in place should be strengthened, and there is the potential that the cleaning validation deficiencies may require that additional conformance lots be manufactured prior to approval. There are also other issues of concern given the number and severity of the 483 observations. It was agreed within the team and by management that we would require three additional conformance lots for approval.
- The fill facility was not inspected and there are information request responses pertaining to this facility that have not yet been reviewed. A complete review of Dynavax's responses is needed to confirm that the fill facility is adequate.
- An overview was provided to the review team on the process, policies, and regulations related to regulatory review of adjuvant facilities; how inspection decisions are made; and whether or not to inspect an adjuvant facility on a new BLA. On the basis of this policy, Avecia, the facility that manufactures the adjuvant, will not be inspected. The primary reasons behind this decision are that Avecia has an existing satisfactory inspectional history; and that the adjuvant is (b) (4) with the product into the final container.

3.3 **Testing:** The sponsor requested a telecon to discuss the samples, reagents and qualification reports. The conformance lots will need to be tested before they are released

Release Testing/Protocols: * Key Issue - We have not received samples or reagents to begin any testing. This could cause a problem if samples arrive too late.

- We sent Dynavax templates for the lot release protocol on August 16 and are waiting for them to submit a draft to the BLA.
- A draft testing plan has been started.
- We working on the final version of the review memo for Sterility and Bioburden tests, there are no issues.

Product Quality: Based on the review of the documents submitted in the BLA a number of issues with regard to adequacy of the method and its validation were found. To complete the review, we requested additional documents from the sponsor. We received some additional documents from the sponsor and are in the process of reviewing these documents and compiling our comments/ issues for further clarification by the sponsor.

- The review shows several deficiencies for all methods and their validation and an IR was sent to the Sponsor on August 16, 2012.
- The significant issues pointed out in the IR, are discussed below:
 1. We do not agree that the (b) (4) of 1018 ISS Adjuvant by (b) (4) method has been adequately validated. The reasons include (1) the results did not meet sponsor's own acceptance criteria, and (2) several impurities (b) (4) with the main compound, 1018 ISS Adjuvant.
 2. There are several significant issues with (b) (4) of Oligonucleotides by (b) (4) method, including (b) (4) for the Accuracy study.
 3. The method Accuracy is inferred without any study performed.
 4. Several documents were referenced in the validation studies for critical data but such documents were not included.
- At this point, we received the requested documents (Item # 4) above (Question #1 of the IR), which are being reviewed. We are waiting for the response to the rest of the rest of the questions (#2-12 of the IR).
- Delayed response to the IR from the sponsor will be a significant issue in terms of completing the review in a timely manner. Lack of adequate validation for the impurity test and lack of accuracy study in method validation for some of the other tests are also critical issues.

3.3 Toxicology

No major concerns about the preclinical immunology studies of this submission were raised.

The nonclinical program included studies to assess the pharmacological properties and toxicity profile of both HBsAg Drug Substance plus 1018 ISS Adjuvant, or of 1018 ISS Adjuvant alone. Pharmacology studies established the effectiveness and dose response of 1018 ISS Adjuvant as an adjuvant for HBsAg Drug Substance. No severe toxicity was observed in studies of the HBsAg Drug Substance combined with 1018 ISS Adjuvant and all effects were consistent with known class effects. A multi-generation reproductive toxicity using a 25-fold excess relative to the human dose for HBsAg Drug Substance and

a 200-fold excess relative to the human dose for 1018 ISS Adjuvant did not identify adverse effects on any of the parameters evaluated. Studies of 1018 ISS Adjuvant alone using a 272-fold excess to the human dose demonstrated rapid elimination of 1018 ISS Adjuvant from the plasma and produced expected class specific toxicities.

3.5 Clinical

Efficacy: HEPLISAV is a two dose regimen of recombinant rHBsAg vaccine plus 1018ISS adjuvant given intramuscularly at 0 and 1 month, proposed for the prevention of all subtypes of hepatitis B infection in adults. HEPLISAV was evaluated in two pivotal phase 3 studies (DV2-HBV-10 and -16; N=3789), three supportive efficacy studies and seven supportive safety studies (see Section 4.0 Overview of Clinical Studies). Immunogenicity of HEPLISAV was assessed by determining the seroprotective rate (SPR): the proportion of subjects with an anti-HbsAg level ≥ 10 mIU/mL. The SPR of HEPLISAV was compared to an active comparator, the licensed hepatitis B vaccine Engerix-B, in both pivotal studies. The immune response seen with HEPLISAV was rapid and robust with > 90% of healthy adult subjects protected against hepatitis B at 48 weeks after the last dose of vaccine (Study DV2-HBV-16). The reviewers concluded that HEPLISAV immunogenicity met the pre-specific criteria for non-inferiority when compared to the licensed hepatitis-B vaccine, Engerix-B.

Safety: The safety evaluation comprised an evaluation of local and systemic reactogenicity, solicited and unsolicited adverse events, and in the pivotal study DV2-HBV-16, prospective analysis for autoimmune events. Most adverse events (AEs) were related to local reactogenicity and were described as mild in intensity. One case each of vasculitis in the HEPLISAV treatment arm (c-ANCA positive Wegener's granulomatosis) and Engerix-B treatment arm (p-ANCA positive vasculitis) and one case of Guillain-Barre syndrome in the HEPLISAV arm, respectively were identified in pivotal study DV2-HBV-16 which prompted a closer examination for autoimmune adverse events in Study DV2-HBV-16. The review of the safety data from these two Phase 3 trials and seven supportive trials is ongoing at this time.

PeRC: PeRC meeting held on October 3, 2102. Full waiver granted for the pediatric studies.

VRBPAC: Planned for Nov 15, 2012. Subject matter experts have been appointed. Hepatitis vaccine expert: Trudy Murphy M.D., CDC, Division of Viral Hepatitis and adjuvant expert: Bali Palundrun M.D., Emory University, School of Medicine.

3.6 Statistical

Stat Reviewer's Main Conclusions and Recommendations:

1. Overall, the BLA demonstrated that, in both pivotal studies, the primary immunogenicity endpoint of seroprotection with HEPLISAV vaccine met the non-inferiority criterion when compared with Engerix-B vaccine. From Table 1.1.1, with the observed SPRs in the HEPLISAV and Engerix-B arms being respectively 95.1% and 81.1%, the 95% CI lower limit of the difference (HEPLISAV – Engerix-B) was +10.7% in study DV2-HBV-10. In study DV2-HBV-16, such observed lower limit was +14.6%.

Both of these lower limits far exceeded the pre-specified margin of -10% supporting the HEPLISAV's non-inferiority in both studies.

2 The BLA stated that the clinical lot consistency criterion which requires the GMC ratios in three lot-pairs to exclude both a 2/3-fold decrease and 3/2-fold increase could not be met by the pre-specified endpoint of immunogenicity measurements at 4 weeks post last dose (i.e., Week 8) of the HEPLISAV vaccine. However, after data unblinding and analysis, the sponsor reached the conclusion that the lot consistency was met at Week 12 of the measurements, which is a post-hoc endpoint. The sponsor's calculations for the post-hoc endpoint were verified and found conforming with the reviewer's results. But the concern for the post-hoc change in the endpoint's measurement Week remains. As a review issue this entails the question of data integrity per GCP. A likely remedy may be to consider another lot consistency study, at least on a pilot scale. But it is up to the OVRP to make the final call and rule.

3. Immunogenicity bridging was a secondary objective. The BLA, overall, indicates comparable immunogenicities between the old lot TDG006 and the combined three new consistency lots of HEPLISAV, in terms of GMCs (Table 3.5.1). In per-protocol population, the GMC ratios (new vs old lot) excluded both a 2/3-fold decrease and a 3/2-fold increase, supporting the bridging of immunogenicity results at both time points of Week 8 and Week 12. In the MITT population and at these same time points, the respective GMC ratios and confidence bounds were 1.21 (95% CI: 0.95, 1.55) and 1.20 (95% CI: 0.98, 1.47), showing the observed upper bound of 1.55 exceeded the 3/2-fold increase at Week 8.

4. The excess rate of seroprotection rate in the HEPLISAV arm compared to Engerix-B persisted regardless of the subject's demographic characteristics and as well at different Weeks of measurements. The details are provided in Table 3.3.2 following dominant categories of age, gender and race and in Table 3.3.3.

5. As with the seroprotection rate, the HEPLISAV vaccinees showed increased GMC as well compared to the Engerix-B vaccinees, over the study Weeks. The GMC with HEPLISAV rose fast at Week 8 and slowed only at Week 36 and later. Comparatively, the GMC with Engerix-B had much slower rise and ran lower (Table 2.3.4 and Table 3.3.6).

3.7 **BiMo**

Inspection assignments were issued on August 24, 2012 to inspect two clinical investigators conducting investigations at sites #22, #23, #24, #25, #26 and #38. The **inspections are pending** and a review will be conducted after the completion of the inspections and the receipt of the inspection reports

3.8 **Epidemiology/Postmarketing: Safety concerns**

- There are no important identified safety issues.
- It was noted that the sponsor did not provide data supporting use of this product in pregnant and lactating women.
- The sponsor proposes to use routine pharmacovigilance activities to monitor safety.

- The sponsor has not proposed enhanced pharmacovigilance activities.

The sponsor proposes a Phase IV prospective, observational cohort study in a total of 10,000 subjects aged 18 years and older enrolled in a US HMO who received at least one HEPLISAV or ENGERIX-B vaccination, as *"one possible approach to further define the safety profile of HEPLISAV. The study will assess the incidence of medically significant adverse events, including autoimmune disease, during the 12 months following first vaccination with HEPLISAV compared with ENGERIX-B...The study will enable an assessment of the RR of medically significant adverse events (AEs)... Data collection will begin 1 year after approval of HEPLISAV in the US...The study report is anticipated to be available 4 years after the start of the data collection."*

- Final determination of the safety profile of the product used in the studies submitted to this BLA is pending final clinical, statistical, and product reviews.
- Product not previously licensed.
- At this time, the reviewer finds no actual or potential safety issues that would require a PMR or REMS.

Recommendations:

- A. Routine pharmacovigilance, including the sponsor's proposal that *"all reports of exposure to HEPLISAV during pregnancy will be followed up to the outcome."*
- B. Enhanced pharmacovigilance to provide expanded AE reporting to the Vaccine Adverse Event Reporting System (VAERS) for one year following product licensure: as 15 day reports, all serious events, whether expected/labeled or unexpected/unlabeled; as 30 day (monthly) reports if not already submitted as 15 day reports: all allergic events, including anaphylaxis; neurological events including Bell's palsy, Guillain-Barre Syndrome, acute disseminated encephalomyelitis; pulmonary embolism, hypothyroidism, Grave's Disease, Wegener's granulomatosis, systemic lupus erythematosus, Sjogren's syndrome, dermatomyositis, rheumatoid arthritis, vasculitis, psoriasis, erythema nodosum, vitiligo; thrombocytopenia, neutropenia, new onset bleeding diathesis; and all cases of new onset autoimmune disease. This will be in addition to filing quarterly periodic safety reports for three years following product licensing.
- C. Review sponsor's proposed post-marketing safety study when available.

Additional discussion points

- Post-marketing passive vs active surveillance
- What objective basis can be used to set a number that would detect an increase to detect objective data and safety signals
- What kind of safety signal is needed for a PMR, are clinical concerns enough. Benefits vs limitations of invoking Title 9 vs PMR or PMC.
- Are there concerns regarding administration of this vaccine in pregnant women.

3.9 Proprietary Name/Labeling; Proper Name

Package Insert:

Dynavax informed to remove all superiority claims from the label. A response was received shortly before the meeting but this had not been reviewed. Review of the labeling is still on-going; main review occurs after Midcycle. Currently, there are a few items that stand out.

Proper name proposal:

Hepatitis B Vaccine, Recombinant, Adjuvanted
Hepatitis B Vaccine (Recombinant), Adjuvanted **
Hepatitis B (Recombinant) Vaccine, Adjuvanted

Management agreed to the proper name of Hepatitis B Vaccine (Recombinant), Adjuvanted.

Proprietary name proposal:

The name Heplisav was 'tentatively approved' under the IND. APLB has reviewed the name and finds that the prefix "Hep" misleadingly implies that the vaccine is effective for multiple strains of hepatitis. At this time, Heplisav is unacceptable. PNR memo is drafted and circulating for concurrence. The sponsor should be notified to officially submit a PNR to the BLA.

3.10 Carton, Container/Labeling

- The License Number is missing. (The sponsor should/could call to get their license number in advance).
- The NDCs are missing (The sponsor can retrieve these in advance too).
- All labels are to be listed in the "How Supplied" section of the SPL.
- For consistency, the words "vaccine" and "recombinant" should be with a capital letter..."Vaccine" and "Recombinant" to match all the other products.
- The two tone coloring of the trade name should be removed...21 CFR 610.62 (b) Prominence...contrast in color value between the proper name and trade name and the background is somewhat questionable. As well the fact the trade name is an uppercased name.
- This issue is really noticeable on the vial label. The color for "One 0.5 mL dose" should be the same color as Rx only.
- There is a prominence issue between the proper name and trade name.

3.11 Issues/Questions requiring decision:

- Should the sponsor be required to do two or three conformance lots and at what point is this conveyed to the sponsor.

Management agreed with the review committee that three conformance lots will be required.

3.12 Final Action Status

Contact Dynavax to convey:

1. the response to 483 should be submitted by the end of the month
2. three conformance lots; additionally we want to review the cleaning validation data first
3. a PNR needs to be sent in to the BLA
4. the proper name has been revised to more adequately describe the vaccine