INHOUDSOPGAVE DOSSIER: M-M-R II,

RVG : 17672

poeder u.inj.

Cassette	beeldnummer
2869	34.0

- A ■ Aanvrage
- B ☐ Verzoek nadere inlichtingen + antwoord
- C ☐ EINDRAPPORTEN (Chemisch-Farmacologisch-Klinisch) + deel College-verslag + ev. EEG-advies + oproep zet bedenkingen + verslag hoorzitting
- D1 ☐ Tegemoetkomende bedenkingen + SLOTRAPPORTEN + ev.deel College-verslag + uitgaande correspondentie
- D2 ☐ Tegemoetkomende bedenkingen + SLOTRAPPORTEN + ev.deel College-verslag + uitgaande correspondentie
- D3 ☐ Tegemoetkomende bedenkingen + SLOTRAPPORTEN + ev.deel College-verslag + uitgaande correspondentie
- D4 ☐ Tegemoetkomende bedenkingen + SLOTRAPPORTEN + ev.deel College-verslag + uitgaande correspondentie
- D5 ☐ Tegemoetkomende bedenkingen + SLOTRAPPORTEN + ev.deel College-verslag + uitgaande correspondentie
- E ☐ Wijzigingen vóór inschrijving + correspondentie
- F ☐ INSCHRIJVING (Bericht + IB + ev. aanbiedingsbrief)
- G ☐ Wijzigingen na inschrijving + correspondentie
- H ☐ Wijzigingen na inschrijving + correspondentie
- I ☐ Wijzigingen na inschrijving + correspondentie
- J ☐ Wijzigingen na inschrijving + correspondentie
- K ☐ Wijzigingen na inschrijving + correspondentie
- L ☐ Wijzigingen na inschrijving + correspondentie
- M ☐ Wijzigingen na inschrijving + correspondentie
- N ☐ Wijzigingen na inschrijving + correspondentie
- O ☐ Wijzigingen toegelaten produkten
- P ☐ Wijzigingen toegelaten produkten
- Q ☐ Wijzigingen toegelaten produkten
- R ☐ Wijzigingen toegelaten produkten
- S ☐ Wijzigingen toegelaten produkten
- T ☐ Wijzigingen toegelaten produkten
- U ☐ Verzoek doorhaling + bericht doorhaling
- V ☐ Verzoek intrekking + bevestigingsbrief
- W ☐ ....
- X ☐ ....
- Y ☐ Nagezonden literatuur
- Z ☐ ....

A

M-M-R II

3 DEC. 1993
17672

DEEL IA - ADMINISTRATIEVE GEGEVENS

[redacted] C

Plaats: HAARLEM

Datum: 2 december 1993

Manager Pharmaceutical Registration
(Functie en handtekening (en) van de aanvrager)

Deze aanvraag betreft:

■ Een nationale aanvraag (nummer (indien beschikbaar):
o Een EG-aanvraag overeenkomstig Richtlijn 83/570/EEG (meerlanden-procedure) rapporteur:
o Een EG-aanvraag overeenkomstig Richtlijn 87/22/EEG (overleg-procedure) rapporteur:
  o Lijst A
  o Lijst B
    datum van goedkeuring als produkt van lijst B door CPMP

o Een aanvraag waarbij wordt verwezen naar een eerdere aanvraag: (produkt, nummer vergunning)

o Overlegprocedure met betrekking tot een wijziging: Nummer advies van de overlegprocedure waarop deze aanvraag betrekking heeft/nationale nummer aanvraag:

o Een opnieuw ingediende aanvraag (nummer voorheen ingediende nationale aanvraag)

. . . . . .

o Een geneesmiddel met een nieuwe werkzame stof
o Een geneesmiddel met een nieuwe combinatie van bekende werkzame stoffen
o Een geneesmiddel met een nieuwe indicatie
o Een andere aanvraag (geef omschrijving, bijvoorbeeld een nieuwe farmaceutische vorm of een nieuwe sterkte)

. . . . . .

o Een vereenvoudigde aanvraag
o o overeenkomstig Richtlijn 65/65, artikel 4, punt 8a) i)
(schriftelijke toestemming van de houder van de vergunning voor het oorspron- kelijke geneesmiddel meezenden)
o overeenkomstig Richtlijn 65/65, artikel 4, punt 8a) ii)
o overeenkomstig Richtlijn 65/65, artikel 4, punt 8a) iii)
(er dient te worden aangetoond dat een in wezen gelijkwaardig produkt minstens zes/tien jaar volgens de geldende communautaire bepalingen in de Gemeenschap is toegelaten en in de lidstaat waarvoor de aanvraag wordt ingediend, in de handel wordt gebracht)
o "hybride" aanvragen (overeenkomstig III/3879/90):
  o ander zout/ester/derivaat
  o ander therapeutisch gebruik
  o andere toedieningsvorm
  o ander doseringsregime
  o andere sterkte
  o produkten met hogere biologische beschikbaarheid
  o overige

---

1. Voorgestelde naam van het geneesmiddel in de betrokken Lidstaat:

Indien bij een communautaire procedure verschillende namen in verschillende lidstaten worden voorgesteld, moeten deze worden vermeld:

Land: Nederland Naam: M-M-R II

[redacted] D

1.1 Naam van het werkzame bestanddeel of de werkzame bestanddelen
(Europese Farmacopee, Nationale Farmacopee, INN, triviale naam en chemische beschrijving)

Verzwakt bofvirus, mazelenvirus, rubellavirus

1.2 Farmacotherapeutische indeling (volgens ATC-indelingssysteem, (Collaborating Centre for Drug Statistics Methodology van de WHO)

Vaccin

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2. Farmaceutische vorm en sterke (volgens de standaardtermen van het CPMP document III/3593/91)

Poeder voor injectie

2.1 Toedieningsweg (volgens de standaardtermen van het CPMP document III/3593/91):

subcutaan

2.2 Verpakking, sluiting en toedieningshulpmiddel (volgens de standaardtermen van het CPMP document III/3593/91)

Injectieflacon met rubberstop,
injectiespuit

2.2.1 Verpakkingsgrootte

1 flacon gevriesdroogd poeder met 1 voorgevulde injectiespuit met oplosmiddel (0,5 ml)

2.2.2 Houdbaarheidstermijn

2 jaar

2.2.3 Houdbaarheidstermijn (na eerste opening van de verpakking)

nvt.

2.2.4 Houdbaarheidstermijn (na reconstitutie)

8 uur

2.2.5 Wijze van bewaren

Bewaar tussen 2-8 °C

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3. Aanvrager (= voorgestelde houder van de vergunning/voorgestelde persoon die verantwoordelijk is voor het in de handel brengen van het geneesmiddel):

Naam : Merck Sharp & Dohme B.V.
Adres : Postbus 581 2003 PC Haarlem
Land : Nederland
Telefoonnummer : 023-153153
Faxnummer : 023-323422

3.2 Contactpersoon die gemachtigd is tijdens de procedure namens de aanvrager op te treden:

C

Naam : Drs. [redacted], apotheker
Adres : zie 3.
Land :
Telefoonnummer :
Faxnummer :

3.3 Contactadres en adres voor het in de handel brengen van het produkt na verlening van de vergunning, indien verschillend van 3./3.2

Naam : nvt.
Adres :
Land :
Telefoonnummer :
Faxnummer :

3.4 Fabrikanten van het eindprodukt en produktie-adressen (inclusief een beschrijving van de produktiestappen die zij uitvoeren en het adres van de "qualified person"

A14

Naam : [redacted]
Adres :
Land :
Telefoonnummer :
Faxnummer :

Naam :
Adres :
Land :
Telefoonnummer :
Faxnummer :

3.4.1 Opslaglokatie:

A14

Naam : [redacted]
Adres :
Land :
Telefoonnummer :
Faxnummer :

3.5 Fabrikant/importeur die verantwoordelijk is voor het vrijgeven van de partijen in de EEG:

Naam : Merck Sharp & Dohme B.V.
Adres : zie 3.4.1
Land :
Telefoonnummer :
Faxnummer :

3.6 Fabrikant(en) van het werkzame bestanddeel of de werkzame bestanddelen:

Naam : Merck & Co.,Inc.
Adres : Sumneytown Pike, West Point, Pennsylvania 19486
Land : United States of America
Telefoonnummer : (215) 661-5000
Faxnummer : (215) 661-7697

Nummer Drug Master File (indien van toepassing): nvt.
Indieningsdatum:

3.7 Bij de ontwikkeling betrokken loonbedrijven:

Vermeld voor elk loonbedrijf: nvt.

Naam :
Adres :
Land :
Telefoonnummer :
Faxnummer :

Volgens het contract uitgevoerde werkzaamheden:

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4. Kwalitatieve en kwantitatieve samenstelling, zowel met betrekking tot het werkzame bestanddeel of de werkzame bestanddelen als met betrekking tot het excipiënt of de excipiënten.
Vermeld hierbij op welke hoeveelheid de samenstelling betrekking heeft (bijvoorbeeld per capsule).
Gelieve de werkzame bestanddelen en de excipiënten gescheiden van elkaar te vermelden.

Nummer	Naam	Hoeveelheid	Eenheid	Norm/verwijzing naar normen
	Werkzame bestanddelen			
1	mazelenvirus	1000 $TCID_{50}$		
2	bofvirus	20000 $TCID_{50}$		
3	rubellavirus	1000 $TCID_{50}$		
	excipiënten			
1	neomycine			
2	sorbitol			
3	gehydroliseerd gelatine			
4	water v. inj.	ad 0,5 ml		

Bijzonderheden omtrent eventuele overmaten: deze dienen niet bij de tabellarisch opgegeven formulering, maar hieronder apart te worden vermeld.	
	- werkzame bestanddelen
	- excipiënten

7. Aanvragen om dit geneesmiddel in de EEG in de handel te brengen (d.w.z. ingediend door hetzelfde bedrijf of een dochter/zuster/moederbedrijf van dezelfde vennootschap/participatiemaatschappij of licentiehouder met hetzelfde werkzame bestanddeel voor een vergelijkbare indicatie)

Aanvaard:	Land: Datum vergunning: Nummer vergunning: Naam produkt:
In behandeling	Land: Datum indiening: Nummer aanvraag: Naam produkt:
Ingetrokken (door aanvrager vóór aanvaarding)	Land: Datum intrekking: Nummer aanvraag: Naam produkt: Reden intrekking:
Ingetrokken (door aanvrager na aanvaarding)	Land: Datum intrekking: Nummer vergunning: Naam produkt: Reden intrekking:
Geschorst/doorgehaald (door bevoegde instantie)	Land: Datum van schorsing/ doorhaling: Nummer vergunning: Naam produkt: Reden van schorsing/ doorhaling:

9.1 Bereidingsvergunning(en) zoals bedoeld in art. 16 van Richtlijn 65/65/EEG (of een equivalent indien bereiding buiten de EEG plaatsvindt).

Zie bijlage.

Inhoudsopgave van de rest van het dossier

Deel I b - Samenvatting van de produktkenmerken

Documentatie	Plaats in het dossier
1. Samenvatting van de produktkenmerken, zoals voorgesteld door de aanvrager, in de taal of talen van de betreffende lidstaat Tevens bijsluiter	Deel I B
2. Tekstvoorstellen (met monsters of modellen) voor: - verpakking - etikettering in de taal of talen van de betreffende lidstaat	Niet aanwezig omdat M-M-R II niet in de handel is

A13

SAMENVATTING VAN DE PRODUKTKENMERKEN

Deel I B

DRT-MMR-I-0191

1 NAAM VAN HET GENEESMIDDEL

M-M-R® II

2 KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING

'M-M-R' II is een vaccin van levende virussen ter immunisatie tegen mazelen (morbilli), bof en rodehond (rubella).

'M-M-R' II is een steriel, gevriesdroogd preparaat van:
(1) 'Attenuvax' (verzwakt levend-mazelenvirusvaccin), een verder verzwakt mazelenvirus dat afkomstig is van de verzwakte edmonstonstam en wordt gekweekt in celculturen van kippeëmbryo's;
(2) 'Mumpsvax' (levend-bofvirusvaccin), de Jeryl Lynnbofstam (B), gekweekt in celculturen van kippeëmbryo's en
(3) 'Meruvax' II (levend-rodehondvirusvaccin), de Wistar RA 27/3-stam van verzwakt, levend-rubellavirus, gekweekt in humane diploïde-celculturen (WI-38). De vaccinvirussen zijn dezelfde als die welke gebruikt worden bij de bereiding van 'Attenuvax' (verzwakt, levend-mazelenvirusvaccin), 'Mumpsvax' (levendbof virusvaccin) en 'Meruvax' II (levend-rubella-virusvaccin). De drie virussen worden gemengd voordat ze worden gevriesdroogd.

Bij bereiding volgens de gebruiksaanwijzing is de te injecteren dosis 0,5 ml en bevat ze minstens het equivalent van 1000 $TCID_{50}$ (tissue culture infectious doses) van het Amerikaanse standaardmazelenvirus, 20000 $TCID_{50}$ van het Amerikaanse standaardbofvirus en 1000 $TCID_{50}$ van het Amerikaanse standaardrubella virus.

3 FARMACEUTISCHE VORM

[redacted]

4. KLINISCHE GEGEVENS

4.1 Therapeutische indicaties

'M-M-R' II is geïndiceerd voor gelijktijdige immunisatie tegen mazelen, bof en rodehond van personen van 15 maanden en ouder. Een tweede dosis van 'M-M-R' II of monovalent mazelenvaccin wordt aanbevolen.

Zuigelingen onder de 15 maanden reageren mogelijk niet op de mazelencomponent van het vaccin daar zij nog van de moeder afkomstige antistoffen tegen mazelen in de circulatie hebben; hoe jonger het kind, des te kleiner is de kans op seroconversie. In afgelegen gebieden, bij andere betrekkelijk onbereikbare bevolkingsgroepen waarvoor vaccinatie programma's organisatorisch moeilijk zijn en bij populaties waarin een infectie met natuurlijke mazelen bij een groot percentage zuigelingenvoor de leeftijd van 15 maanden kan optreden, kan het gewenst zijn het vaccin aan zuigelingen op jongere leeftijd toe te dienen. Baby's die in hun eerste levensjaar onder deze omstandigheden werden gevacci-neerd, moeten, nadat ze 15 maanden oud zijn geworden, opnieuw worden ingeënt. De meeste zuigelingen van 12 tot 14 maanden reageren prompt, maar een herha-lingsinjectie bij het naar school gaan of daarna kan nodig zijn om bij deze kinderen een doorbraakinfectie te voorkomen. Er zijn enige aanwijzingen dat baby's die onder de leeftijd van een jaar zijn gevaccineerd, mogelijk geen aanhoudende antistoftiter ontwikkelen wanneer zij later worden gehervaccineerd. Het voordeel van een vroege bescherming moet tegen de kans op het uitblijven van een adequaat reactie op hervaccinatie worden afgewogen.

Nog niet gevaccineerde kinderen van vatbare zwangere vrouwen dienen met levend, verzwakt rubellavaccin te worden ingeënt omdat een gevaccineerd kind minder kans loopt natuurlijke rubella te krijgen en het virus in het gezin te introduceren.

Niet-zwangere adolescente en volwassen vrouwen
Vaccinatie van vatbare niet-zwangere adolescente en volwassen vrouwen in de vruchtbare leeftijd met een verzwakt, levend-rodehondvirusvaccin is geïndiceerd als bepaalde voorzorgen in acht worden genomen (zie hierna en onder Voorzorgen). Vaccinatie van vatbare vrouwen na de puberteit geeft individuele bescherming tegen het daarna verwerven van een infectie met rodehond tijdens de zwangerschap, wat weer verhindert dat de foetus geïnfecteerd wordt en dat er aangeboren rubella-afwijkingen ontstaan.

Vrouwen in de vruchtbare leeftijd dient te worden geadviseerd drie maanden na de vaccinatie niet zwanger te worden en zij dienen van de reden van deze voorzorg op de hoogte te worden gesteld. (Aanbeveling van het Immunization Practices Advisory Committee (ACIP): „Gezien het belang van bescherming van deze leeftijdsgroep tegen rubella is het in een rubella-immunisatieprogramma een redelijke voorzorg de vrouwen te vragen of zij zwanger zijn, degenen die zeggen dat zij zwanger zijn, uit te sluiten, en de theoretische risico's aan de overigen uiteen te zetten.")

Aanbevolen wordt de vatbaarheid voor rubella voor vaccinatie vast te stellen door serologisch onderzoek. (Het Immunization Practices Advisory Committee (ACIP) heeft het volgende verklaard: „Bij vrouwen in de vruchtbare leeftijd die voor vaccinatie in aanmerking komen, kan, als zulks uitvoerbaar is en als er betrouwbare laboratoriumvoorzieningen beschikbaar zijn, serologisch onderzoek worden verricht om de vatbaarheid voor rubella vast te stellen ... Het routinematig uitvoeren van serologisch onderzoek bij alle vrouwen in de vruchtbare leeftijd ter bepaling van de vatbaarheid opdat het vaccin uitsluitend aan vatbaar gebleken personen wordt toegediend, is echter kostbaar en is in sommige gebieden ineffectief geweest. Derhalve meent het ACIP dat inenting tegen rubella van een vrouw van wie niet bekend is of zij zwanger is en die niet eerder is gevaccineerd, zonder serologisch onderzoek gerechtvaardigd is."

Aangeboren afwijkingen komen bij maximaal 7 % van alle levend geborenen voor. Als deze zich toevallig na toediening van het vaccin mochten voordoen, zou zulks tot een verkeerde uitleg van de oorzaak aanleiding kunnen geven, vooral als de immunologische status van de gevaccineerden voor de rubellavaccinatie onbekend is.

Vrouwen na de puberteit dienen op de hoogte te worden gesteld van het frequent voorkomen van vanzelf overgaande artralgie en eventuele artritis, die twee à vier weken na vaccinatie beginnen (zie Bijwerkingen).

Vrouwen post partum
Het is in vele gevallen praktisch gebleken voor rodehond vatbare vrouwen in de periode onmiddellijk na de partus te vaccineren (zie 'Gebruik in de zwangerschap en en het geven van borstvoeding').

Hervaccinatie
Kinderen die voor de eenjarige leeftijd werden gevaccineerd, dienen op de leeftijd van 15 maanden opnieuw te worden ingeënt.
Aan kinderen die voor het eerst gevaccineerd zijn op een leeftijd van 15 maanden of ouder, wordt aanbevolen een tweede vaccinatie te geven op ongeveer 9-jarige leeftijd.

4.2 Dosering en wijze van toediening

Voor subcutane toediening.

Niet intraveneus injecteren
De dosering van het vaccin is voor alle personen dezelfde. Injiceer de gehele inhoud van het flaconnetje met één dosis (ca. 0,5 ml) of 0,5 ml van het gerede vaccin uit de flacon met 10 doses subcutaan, liefst lateraal in de bovenarm.

Flaconnetje à een dosis
Zuig eerst de gehele hoeveelheid van het oplosmiddel in de voor oplossing te

gebruiken spuit. Spuit al het in de spuit aanwezige oplosmiddel in het flaconnetje met het gevriesdroogde vaccin; dit goed schudden om een grondige vermenging te verkrijgen. Zuig de gehele hoeveelheid in een spuit op en injecteer de gehele hoeveelheid van het opgeloste vaccin subcutaan.

Gebruik voor de oplossing van het vaccin uitsluitend het meegeleverde oplosmiddel want dit is vrij van conserveermiddelen en andere antivirale stoffen die het vaccin zouden kunnen inactiveren.

Flacon à 10 doses (uitsluitend beschikbaar voor overheidsinstellingen)
Zuig de gehele hoeveelheid (7 ml) van de flacon met het oplosmiddel in de steriele, voor oplossing te gebruiken spuit en spuit deze in de flacon à 10 doses gevriesdroogd vaccin. Goed schudden om een grondige vermenging te verkrijgen. Op het etiket staat: „Voor gebruik met een injectiepistool of injectiespuit". Het gebruik van aparte steriele spuiten voor flacons met 10 doses of minder is toegestaan. Het vaccin en het oplosmiddel bevatten geen conserveermiddelen; daarom dient de gebruiker het risico van verontreiniging voor ogen te houden en speciale voorzorgen te nemen om de steriliteit en de werkzaamheid van het produkt te waarborgen. De toepassing van aseptische methodes en een juiste bewaring voor en na reconstitutie van het vaccin om er individuele doses uit te halen, is noodzakelijk. Gebruik 0,5 ml van het opgeloste vaccin voor subcutane injectie.

Het is belangrijk voor elke patiënt een aparte gesteriliseerde spuit en naald te gebruiken ter voorkoming van het overbrengen van hepatitis B en andere infectieuze stoffen van de ene persoon op de andere.

Parenterale geneesmiddelen dienen voor toediening op vaste deeltjes en verkleuring te worden geschouwd. Na oplossing is 'M-M-R II' helder geel.

4.3 Contra-indicaties

Zwangeren mogen niet met 'M-M-R'II worden gevaccineerd, daar de eventuele effecten van het vaccin op de ontwikkeling van de foetus nog onbekend zijn. Indien men overgaat tot vaccinatie van vrouwen na de pubertijd, moet zwangerschap de eerste drie maanden na de vaccinatie worden vermeden (Zie gebruik tijdens zwangerschap en het geven van borstvoeding).

Anafylactische of anafylactoïde reactie op neomycine.

Anafylactische of anafylactoïde reactie op eieren in de anamnese (zie Overgevoeligheid voor eieren, hierna).

Alle met koorts gepaard gaande aandoeningen van de luchtwegen en andere actieve, met koorts gepaard gaande infecties.

Actieve, onbehandelde tuberculose.

Patiënten die met immunosuppressiva worden behandeld. Deze contra-indicatie geldt niet voor patiënten die corticosteroïden bij wijze van substitutietherapie krijgen, bijvoorbeeld bij de ziekte van Addison.

Patiënten met bloeddyscrasieën, leukemie, lymphomata van elk type of andere maligne neoplasmata die het beenmerg of het lymfatische systeem aantasten.

Primaire en verworven immunodeficiënties, zoals patiënten met immunosuppressie in samenhang met AIDS of andere klinische manifestaties van infectie met humane immunodeficiëntievirussen; cellulaire immunodeficiëntie, hypogammaglobulinemie en dysgammaglobulinemie.

Patiënten met een aangeboren of erfelijke immunodeficiëntie in hun familie totdat de immunocompetentie van de te vaccineren persoon is vastgesteld.

Overgevoeligheid voor eieren
Levend mazelenvaccin en levend bofvaccin worden in kippeëmbryo's gekweekt. Personen met anafylactische, anafylactoïde of andere directe reacties in de anamnese (zoals

3.2 Contactpersoon die gemachtigd is tijdens de procedure namens de aanvrager op te treden:

Naam : [redacted] C
Adres : zie 3.
Land :
Telefoonnummer :
Faxnummer :

3.3 Contactadres en adres voor het in de handel brengen van het produkt na verlening van de vergunning, indien verschillend van 3./3.2

Naam : nvt.
Adres :
Land :
Telefoonnummer :
Faxnummer :

3.4 Fabrikanten van het eindprodukt en produktie-adressen (inclusief een beschrijving van de produktiestappen die zij uitvoeren en het adres van de "qualified person"

Naam :
Adres :
Land :
Telefoonnummer :
Faxnummer :

[redacted] A14

Naam :
Adres :
Land :
Telefoonnummer :
Faxnummer :

3.4.1 Opslaglokatie:

Naam :
Adres :
Land :
Telefoonnummer :
Faxnummer :

[redacted] A14

3.5 Fabrikant/importeur die verantwoordelijk is voor het vrijgeven van de partijen in de EEG:

Naam : Merck Sharp & Dohme B.V.
Adres : zie 3.4.1
Land :
Telefoonnummer :
Faxnummer :

3.6 Fabrikant(en) van het werkzame bestanddeel of de werkzame bestanddelen:

Naam : Merck & Co.,Inc.
Adres : Sumneytown Pike, West Point, Pennsylvania 19486
Land : United States of America
Telefoonnummer : (215) 661-5000
Faxnummer : (215) 661-7697

Nummer Drug Master File (indien van toepassing): nvt.
Indieningsdatum:

3.7 Bij de ontwikkeling betrokken loonbedrijven:

Vermeld voor elk loonbedrijf: nvt.

Naam :
Adres :
Land :
Telefoonnummer :
Faxnummer :

Volgens het contract uitgevoerde werkzaamheden:

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4. Kwalitatieve en kwantitatieve samenstelling, zowel met betrekking tot het werkzame bestanddeel of de werkzame bestanddelen als met betrekking tot het excipiënt of de excipiënten.
Vermeld hierbij op welke hoeveelheid de samenstelling betrekking heeft (bijvoorbeeld per capsule).
Gelieve de werkzame bestanddelen en de excipiënten gescheiden van elkaar te vermelden.

Nummer	Naam	Hoeveelheid	Eenheid	Norm/verwijzing naar normen
	Werkzame bestanddelen			
1	mazelenvirus	1000 $TCID_{50}$		
2	bofvirus	20000 $TCID_{50}$		
3	rubellavirus	1000 $TCID_{50}$		
	excipiënten			
1	neomycine			
2	sorbitol			
3	gehydroliseerd gelatine			
4	water v. inj.	ad 0,5 ml		

Bijzonderheden omtrent eventuele overmaten: deze dienen niet bij de tabellarisch opgegeven formulering, maar hieronder apart te worden vermeld.	
	- werkzame bestanddelen
	- excipiënten

7. Aanvragen om dit geneesmiddel in de EEG in de handel te brengen (d.w.z. ingediend door hetzelfde bedrijf of een dochter/zuster/moederbedrijf van dezelfde vennootschap/participatiemaatschappij of licentiehouder met hetzelfde werkzame bestanddeel voor een vergelijkbare indicatie)

Aanvaard:	Land: Datum vergunning: Nummer vergunning: Naam produkt:
In behandeling	Land: Datum indiening: Nummer aanvraag: Naam produkt:
Ingetrokken (door aanvrager vóór aanvaarding)	Land: Datum intrekking: Nummer aanvraag: Naam produkt: Reden intrekking:
Ingetrokken (door aanvrager na aanvaarding)	Land: Datum intrekking: Nummer vergunning: Naam produkt: Reden intrekking:
Geschorst/doorgehaald (door bevoegde instantie)	Land: Datum van schorsing/ doorhaling: Nummer vergunning: Naam produkt: Reden van schorsing/ doorhaling:

9.1 Bereidingsvergunning(en) zoals bedoeld in art. 16 van Richtlijn 65/65/EEG (of een equivalent indien bereiding buiten de EEG plaatsvindt).

Zie bijlage.

Inhoudsopgave van de rest van het dossier

Deel I b - Samenvatting van de produktkenmerken

Documentatie	Plaats in het dossier
1. Samenvatting van de produktkenmerken, zoals voorgesteld door de aanvrager, in de taal of talen van de betreffende lidstaat Tevens bijsluiter	Deel I B
2. Tekstvoorstellen (met monsters of modellen) voor: - verpakking - etikettering in de taal of talen van de betreffende lidstaat	Niet aanwezig omdat M-M-R II niet in de handel is

Deel I c - Deskundigenrapporten

Documentatie		Plaats in dossier
A.	Chemisch/Farmaceutisch/Biologisch	
	Zie bijlage	
B.	Toxicologisch-farmacologisch	
	Zie bijlage	
C.	Klinisch	
	Zie bijlage	

A13

SAMENVATTING VAN DE PRODUKTKENMERKEN

Deel I B

DRT-MMR-I-0191

1 NAAM VAN HET GENEESMIDDEL

M-M-R® II

2 KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING

'M-M-R' II is een vaccin van levende virussen ter immunisatie tegen mazelen (morbilli), bof en rodehond (rubella).

'M-M-R' II is een steriel, gevriesdroogd preparaat van:
(1) 'Attenuvax' (verzwakt levend-mazelenvirusvaccin), een verder verzwakt mazelenvirus dat afkomstig is van de verzwakte edmonstonstam en wordt gekweekt in celculturen van kippeëmbryo's;
(2) 'Mumpsvax' (levend-bofvirusvaccin), de Jeryl Lynnbofstam (B), gekweekt in celculturen van kippeëmbryo's en
(3) 'Meruvax' II (levend-rodehondvirusvaccin), de Wistar RA 27/3-stam van verzwakt, levend-rubellavirus, gekweekt in humane diploïde-celculturen (WI-38). De vaccinvirussen zijn dezelfde als die welke gebruikt worden bij de bereiding van 'Attenuvax' (verzwakt, levend-mazelenvirusvaccin), 'Mumpsvax' (levendbof virusvaccin) en 'Meruvax' II (levend-rubella-virusvaccin). De drie virussen worden gemengd voordat ze worden gevriesdroogd.

Bij bereiding volgens de gebruiksaanwijzing is de te injecteren dosis 0,5 ml en bevat ze minstens het equivalent van 1000 $TCID_{50}$ (tissue culture infectious doses) van het Amerikaanse standaardmazelenvirus, 20000 $TCID_{50}$ van het Amerikaanse standaardbofvirus en 1000 $TCID_{50}$ van het Amerikaanse standaardrubella virus.

3 FARMACEUTISCHE VORM

[redacted]

4. KLINISCHE GEGEVENS

4.1 Therapeutische indicaties

'M-M-R' II is geïndiceerd voor gelijktijdige immunisatie tegen mazelen, bof en rodehond van personen van 15 maanden en ouder. Een tweede dosis van 'M-M-R' II of monovalent mazelenvaccin wordt aanbevolen.

Zuigelingen onder de 15 maanden reageren mogelijk niet op de mazelencomponent van het vaccin daar zij nog van de moeder afkomstige antistoffen tegen mazelen in de circulatie hebben; hoe jonger het kind, des te kleiner is de kans op seroconversie. In afgelegen gebieden, bij andere betrekkelijk onbereikbare bevolkingsgroepen waarvoor vaccinatie programma's organisatorisch moeilijk zijn en bij populaties waarin een infectie met natuurlijke mazelen bij een groot percentage zuigelingenvoor de leeftijd van 15 maanden kan optreden, kan het gewenst zijn het vaccin aan zuigelingen op jongere leeftijd toe te dienen. Baby's die in hun eerste levensjaar onder deze omstandigheden werden gevacci-neerd, moeten, nadat ze 15 maanden oud zijn geworden, opnieuw worden ingeënt. De meeste zuigelingen van 12 tot 14 maanden reageren prompt, maar een herha-lingsinjectie bij het naar school gaan of daarna kan nodig zijn om bij deze kinderen een doorbraakinfectie te voorkomen. Er zijn enige aanwijzingen dat baby's die onder de leeftijd van een jaar zijn gevaccineerd, mogelijk geen aanhoudende antistoftiter ontwikkelen wanneer zij later worden gehervaccineerd. Het voordeel van een vroege bescherming moet tegen de kans op het uitblijven van een adequaat reactie op hervaccinatie worden afgewogen.

Nog niet gevaccineerde kinderen van vatbare zwangere vrouwen dienen met levend, verzwakt rubellavaccin te worden ingeënt omdat een gevaccineerd kind minder kans loopt natuurlijke rubella te krijgen en het virus in het gezin te introduceren.

Niet-zwangere adolescente en volwassen vrouwen
Vaccinatie van vatbare niet-zwangere adolescente en volwassen vrouwen in de vruchtbare leeftijd met een verzwakt, levend-rodehondvirusvaccin is geïndiceerd als bepaalde voorzorgen in acht worden genomen (zie hierna en onder Voorzorgen). Vaccinatie van vatbare vrouwen na de puberteit geeft individuele bescherming tegen het daarna verwerven van een infectie met rodehond tijdens de zwangerschap, wat weer verhindert dat de foetus geïnfecteerd wordt en dat er aangeboren rubella-afwijkingen ontstaan.

Vrouwen in de vruchtbare leeftijd dient te worden geadviseerd drie maanden na de vaccinatie niet zwanger te worden en zij dienen van de reden van deze voorzorg op de hoogte te worden gesteld. (Aanbeveling van het Immunization Practices Advisory Committee (ACIP): „Gezien het belang van bescherming van deze leeftijdsgroep tegen rubella is het in een rubella-immunisatieprogramma een redelijke voorzorg de vrouwen te vragen of zij zwanger zijn, degenen die zeggen dat zij zwanger zijn, uit te sluiten, en de theoretische risico's aan de overigen uiteen te zetten.")

Aanbevolen wordt de vatbaarheid voor rubella voor vaccinatie vast te stellen door serologisch onderzoek. (Het Immunization Practices Advisory Committee (ACIP) heeft het volgende verklaard: „Bij vrouwen in de vruchtbare leeftijd die voor vaccinatie in aanmerking komen, kan, als zulks uitvoerbaar is en als er betrouwbare laboratoriumvoorzieningen beschikbaar zijn, serologisch onderzoek worden verricht om de vatbaarheid voor rubella vast te stellen ... Het routinematig uitvoeren van serologisch onderzoek bij alle vrouwen in de vruchtbare leeftijd ter bepaling van de vatbaarheid opdat het vaccin uitsluitend aan vatbaar gebleken personen wordt toegediend, is echter kostbaar en is in sommige gebieden ineffectief geweest. Derhalve meent het ACIP dat inenting tegen rubella van een vrouw van wie niet bekend is of zij zwanger is en die niet eerder is gevaccineerd, zonder serologisch onderzoek gerechtvaardigd is."

Aangeboren afwijkingen komen bij maximaal 7 % van alle levend geborenen voor. Als deze zich toevallig na toediening van het vaccin mochten voordoen, zou zulks tot een verkeerde uitleg van de oorzaak aanleiding kunnen geven, vooral als de immunologische status van de gevaccineerden voor de rubellavaccinatie onbekend is.

Vrouwen na de puberteit dienen op de hoogte te worden gesteld van het frequent voorkomen van vanzelf overgaande artralgie en eventuele artritis, die twee à vier weken na vaccinatie beginnen (zie Bijwerkingen).

Vrouwen post partum
Het is in vele gevallen praktisch gebleken voor rodehond vatbare vrouwen in de periode onmiddellijk na de partus te vaccineren (zie 'Gebruik in de zwangerschap en en het geven van borstvoeding').

Hervaccinatie
Kinderen die voor de eenjarige leeftijd werden gevaccineerd, dienen op de leeftijd van 15 maanden opnieuw te worden ingeënt.
Aan kinderen die voor het eerst gevaccineerd zijn op een leeftijd van 15 maanden of ouder, wordt aanbevolen een tweede vaccinatie te geven op ongeveer 9-jarige leeftijd.

4.2 Dosering en wijze van toediening

Voor subcutane toediening.

Niet intraveneus injecteren
De dosering van het vaccin is voor alle personen dezelfde. Injiceer de gehele inhoud van het flaconnetje met één dosis (ca. 0,5 ml) of 0,5 ml van het gerede vaccin uit de flacon met 10 doses subcutaan, liefst lateraal in de bovenarm.

Flaconnetje à een dosis
Zuig eerst de gehele hoeveelheid van het oplosmiddel in de voor oplossing te

gebruiken spuit. Spuit al het in de spuit aanwezige oplosmiddel in het flaconnetje met het gevriesdroogde vaccin; dit goed schudden om een grondige vermenging te verkrijgen. Zuig de gehele hoeveelheid in een spuit op en injecteer de gehele hoeveelheid van het opgeloste vaccin subcutaan.

Gebruik voor de oplossing van het vaccin uitsluitend het meegeleverde oplosmiddel want dit is vrij van conserveermiddelen en andere antivirale stoffen die het vaccin zouden kunnen inactiveren.

Flacon à 10 doses (uitsluitend beschikbaar voor overheidsinstellingen)
Zuig de gehele hoeveelheid (7 ml) van de flacon met het oplosmiddel in de steriele, voor oplossing te gebruiken spuit en spuit deze in de flacon à 10 doses gevriesdroogd vaccin. Goed schudden om een grondige vermenging te verkrijgen. Op het etiket staat: „Voor gebruik met een injectiepistool of injectiespuit". Het gebruik van aparte steriele spuiten voor flacons met 10 doses of minder is toegestaan. Het vaccin en het oplosmiddel bevatten geen conserveermiddelen; daarom dient de gebruiker het risico van verontreiniging voor ogen te houden en speciale voorzorgen te nemen om de steriliteit en de werkzaamheid van het produkt te waarborgen. De toepassing van aseptische methodes en een juiste bewaring voor en na reconstitutie van het vaccin om er individuele doses uit te halen, is noodzakelijk. Gebruik 0,5 ml van het opgeloste vaccin voor subcutane injectie.

Het is belangrijk voor elke patiënt een aparte gesteriliseerde spuit en naald te gebruiken ter voorkoming van het overbrengen van hepatitis B en andere infectieuze stoffen van de ene persoon op de andere.

Parenterale geneesmiddelen dienen voor toediening op vaste deeltjes en verkleuring te worden geschouwd. Na oplossing is 'M-M-R II' helder geel.

4.3 Contra-indicaties

Zwangeren mogen niet met 'M-M-R'II worden gevaccineerd, daar de eventuele effecten van het vaccin op de ontwikkeling van de foetus nog onbekend zijn. Indien men overgaat tot vaccinatie van vrouwen na de pubertijd, moet zwangerschap de eerste drie maanden na de vaccinatie worden vermeden (Zie gebruik tijdens zwangerschap en het geven van borstvoeding).

Anafylactische of anafylactoïde reactie op neomycine.

Anafylactische of anafylactoïde reactie op eieren in de anamnese (zie Overgevoeligheid voor eieren, hierna).

Alle met koorts gepaard gaande aandoeningen van de luchtwegen en andere actieve, met koorts gepaard gaande infecties.

Actieve, onbehandelde tuberculose.

Patiënten die met immunosuppressiva worden behandeld. Deze contra-indicatie geldt niet voor patiënten die corticosteroïden bij wijze van substitutietherapie krijgen, bijvoorbeeld bij de ziekte van Addison.

Patiënten met bloeddyscrasieën, leukemie, lymphomata van elk type of andere maligne neoplasmata die het beenmerg of het lymfatische systeem aantasten.

Primaire en verworven immunodeficiënties, zoals patiënten met immunosuppressie in samenhang met AIDS of andere klinische manifestaties van infectie met humane immunodeficiëntievirussen; cellulaire immunodeficiëntie, hypogammaglobulinemie en dysgammaglobulinemie.

Patiënten met een aangeboren of erfelijke immunodeficiëntie in hun familie totdat de immunocompetentie van de te vaccineren persoon is vastgesteld.

Overgevoeligheid voor eieren
Levend mazelenvaccin en levend bofvaccin worden in kippeëmbryo's gekweekt. Personen met anafylactische, anafylactoïde of andere directe reacties in de anamnese (zoals

netelroos, zwelling van mond en keel, bemoeilijkte ademhaling, hypotensie en shock) na het eten van eieren dienen niet te worden gevaccineerd. Er zijn aanwij-zingen dat personen geen groter risico lopen als zij een allergie voor eieren hebben die niet anafylactisch of anafylactoïd is. Dergelijke personen dienen op de gebruikelijke wijzen te worden gevaccineerd.

Er zijn geen aanwijzingen dat personen die voor kippen of veren allergisch zijn, een groter risico van een reactie op het vaccin lopen.

4.4 Speciale waarschuwingen en bijzondere voorzorgen bij gebruik

Algemeen
Ter behandeling van een eventuele anafylactische of anafylactoïde reactie dienen adequaat voorzorgen te worden getroffen, waaronder het bij de hand hebben van epinefrine (adrenaline).

Voorzichtigheid is geboden bij toediening van 'M-M-R' II aan personen die geleden hebben aan of een familie-anamnese hebben met convulsies, hersenbeschadiging of andere ziekten, waarbij stress door koorts vermeden moet worden. De arts moet zorgvuldig letten op temperatuurverhoging die na vaccinatie kan ontstaan (zie Bijwerkingen).

Kinderen en jonge volwassenen van wie bekend is dat zij met humane immunodeficiëntie virussen geïnfecteerd zijn maar die geen duidelijke klinische manifestaties van immunosuppressie hebben, mogen worden gevaccineerd; de gevaccineerden dienen echter zorgvuldig te worden gecontroleerd op blootstelling aan door vaccinatie te voorkomen aandoeningen, daar de immunisatie minder doel-treffend kan zijn dan bij niet-geïnfecteerde personen. In geselecteerde gevallen kan het nodig zijn de antistoftiter in de circulatie vast te stellen met het oog op het nemen van de aangewezen beschermende maatregelen, waaronder immunoprofylaxe indien de immuniteit tot een niet-beschermend niveau is afgenomen.

Uitscheiding van geringe hoeveelheden van het levende, verzwakte rubellavirus via neus of keel is bij de meeste vatbare personen 7 tot 28 dagen na vacci-natie opgetreden. Er is geen overtuigend bewijs dat dit virus wordt overgedragen op vatbare personen die met de gevaccineerden in aanraking komen. Dientengevolge wordt overbrenging door nauw persoonlijk contact, hoewel theoretisch mogelijk, niet als een aanzienlijk risico beschouwd.

Overdracht van het rubellavaccinvirus op zuigelingen via de moedermelk is echter gedocumenteerd (zie Gebruik in de zwangerschap en tijdens de lactatie).

Er zijn geen meldingen van de overdracht van verzwakte levende mazelen- of bofvirussen door gevaccineerden op vatbare contactpersonen.

Bij kinderen die behandeld worden voor tuberculose is geen exacerbatie van de ziekte waargenomen na vaccinatie met levend mazelenvirusvaccin. Onderzoekingen naar het effect van mazelenvaccins op onbehandelde tuberculeuze kinderen zijn nog niet gepubliceerd.

Zoals voor elk vaccin geldt, behoeft vaccinatie met 'M-M-R' II niet bij 100% van de vatbare gevaccineerden een seroconversie tot gevolg te hebben.

4.5 Interacties met andere geneesmiddelen en andere vormen van interactie

De vaccinatie moet minstens drie maanden worden uitgesteld na bloed- of plasmatransfusies en na toediening van humaan immuunserumglobuline.

Er zijn gevallen bekend waarin verzwakt, levend-mazelen-, bof- en rubellavirusvaccins bij afzonderlijke toediening de gevoeligheid van de huid voor tuberculine tijdelijk kunnen onderdrukken. Als er een tuberculinereactie gedaan moet worden, moet die derhalve plaatsvinden voor of tegelijk met het toedienen van 'M-M-R' II.

Gebruik met andere vaccins

'M-M-R' II dient minstens één maand voor of na toediening van andere vaccins te worden gegeven.

4.6 Gebruik bij zwangerschap en het geven van borstvoeding

Er zijn met 'M-M-R' II geen voortplantingsonderzoekingen bij dieren verricht. Evenmin is bekend of 'M-M-R' II de foetus bij toediening aan een zwangere kan beschadigen of het voortplantingsvermogen kan beïnvloeden. Daarom dient het vaccin niet aan zwangeren te worden toegediend; voorts dient zwangerschap gedurende drie maanden na de vaccinatie te worden vermeden.

Bij het adviseren van vrouwen die abusievelijk worden gevaccineerd wanneer ze zwanger zijn of die binnen drie maanden na de vaccinatie zwanger worden, dient de arts zich van het volgende bewust te zijn:

1. in een enquête die zich over 10 jaar uitstrekte en ruim 700 zwangeren omvatte die binnen drie maanden voor of na de bevruchting het rubella-vaccin kregen (van wie er 189 de Wistar RA 27/3-stam kregen), had geen van de neonati afwijkingen die met het congenitale rubellasyndroom overeenkwamen;
2. hoewel het bofvirus de placenta en de foetus kan infecteren, is er geen goed bewijs dat het bij mensen aangeboren afwijkingen kan veroorzaken. Ook is gebleken dat het bofvaccinvirus de placenta kan infecteren, maar het virus is niet geïsoleerd uit de vruchtweefsels van vatbare vrouwen die gevaccineerd werden en electieve abortus ondergingen, en
3. vermeld is dat het risico voor de foetus wordt vergroot wanneer een zwangere natuurlijke mazelen krijgt. Een hogere frequentie van spontane abortus, doodgeboren kinderen, aangeboren afwijkingen en prematuren is na natuurlijke mazelen gedurende zwangerschap waargenomen.

Er bestaan geen goede onderzoekingen met de verzwakte mazelenvirusstam (vaccin) in de graviditeit. Het is echter verstandig aan te nemen dat de virusstam in het vaccin ook nadelige effecten op de foetus kan hebben.

Het is niet bekend of het mazelen- of bofvaccinvirus in de moedermelk wordt uitgescheiden. Uit recent onderzoek is gebleken dat vrouwen die borstvoeding geven, die na de partus met verzwakt, levend rodehondvaccin zijn gevaccineerd, het virus met de moedermelk kunnen afscheiden en het kunnen overdragen aan zuigelingen die borstvoeding krijgen. Geen van de zuigelingen met serologische aanwijzingen van een rubella-infectie had een ernstige ziekte, maar één vertoonde een voor verworven rubella kenmerkende lichte klinische aandoening. 'M-M-R' II dient met de nodige voorzichtigheid aan een vrouw die borstvoeding geven te worden toegediend.

4.7 Beïnvloeding van de rijvaardigheid en het vermogen om machines te gebruiken

Er zijn geen specifieke gegevens. Enkele van de effecten genoemd onder 'Bijwerkingen', zoals hoofdpijn, duizeligheid en optische stoornissen kunnen de rijvaardigheid of het vermogen om machines te gebruiken, beïnvloeden.

4.8. Bijwerkingen

<u>Algemeen optredend</u>

Een kortdurend gevoel van branden en/of steken op de injectieplaats.

<u>Af en toe optredend</u>

Lichaam als geheel: koorts (38,3 °C of hoger)

Huid: exantheem, doorgaans minimaal maar kan gegeneraliseerd zijn. Over het algemeen verdwenen de koorts, het exantheem of beide tussen de vijfde en twaalfde dag.

<u>Zelden</u>

Lichaam als geheel: lichte plaatselijke reacties zoals erytheem, induratie en gevoeligheid; keelpijn, malaise

Spijsverteringsstelsel: parotitis, misselijkheid, braken, diarree

Bloed/lymfe: plaatselijke lymfadenopathie, trombocytopenie, purpura

Overgevoeligheid: allergische reacties zoals kwaddel en/of hof op de injectieplaats, anafylaxie en anafylactoïde reacties, urticaria

Bewegingsapparaat: artralgie en/of artritis (gewoonlijk voorbijgaand en zelden chronisch), myalgie

Zenuwstelsel/psychiatrische: koortsstuipen bij kinderen, convulsies of stuipen zonder koorts, hoofdpijn, duizeligheid, paresthesieën, polyneuritis, het syndroom van Guillain-Barré, ataxie. Encefalitis/encefalopathie zijn ongeveer eenmaal op elke 3 miljoen doses vermeld. In geen enkel geval is gebleken dat de reacties in feite door het vaccin werden veroorzaakt. Het risico van dergelijke ernstige neurologische stoornissen na toediening van een levend-mazelenvirusvaccin blijft veel minder dan dat van encefalitis en encefalo-pathie door natuurlijke mazelen (een op de 2000 vermelde gevallen).

Huid: erythema multiforme

Zintuigen: vormen van neuritis optica, waaronder neuritis retrobulbaris, papillitis en retinitis; oogspierverlamming, otitis media, neurale doofheid, conjunctivitis

Urogenitaal: orchitis

Er zijn meldingen van subacute scleroserende panencefalitis (SSPE) bij kinderen die geen natuurlijke mazelen in de anamnese hadden maar wel tegen mazelen werden gevaccineerd. Enkele van deze gevallen zijn mogelijk het gevolg van niet-onderkende mazelen in het eerste levensjaar of eventueel van de mazelenvaccinatie. Op basis van de geschatte nationale distributie van mazelenvaccin is de samenhang tussen de SSPE-gevallen en de mazelenvaccinatie circa één geval op de miljoen gedistribueerde doses vaccins. Dit is veel minder dan het verband met natuurlijke mazelen: 6-22 SSPE-gevallen per miljoen gevallen van mazelen. Uit een door het Center for Disease Control verricht retrospectief, gecontroleerd onderzoek komt naar voren dat als gevolg van de mazelenvaccinatie een goede bescherming tegen SSPE werd verkregen doordat mazelen, met hun inherente grotere risico van SSPE, werden voorkomen.

Lokale reacties die gekenmerkt zijn door duidelijke zwelling, roodheid en blaasvorming op de plaats van de injectie met verzwakte, levende-mazelen-virusvaccins en systemische reacties waaronder atypische mazelen, zijn voorgekomen bij personen die voordien al met een vaccin van gedood mazelenvirus werden ingeënt. 'M-M-R' II werd zo in klinisch onderzoek niet gegeven. Zelden zijn ernstigere reacties die ziekenhuisopname vereisten, waaronder aanhoudend hoge koorts, panniculitis en uitgebreide lokale reacties, vermeld.

Artralgie en/of artritis (gewoonlijk voorbijgaand en zelden chronisch) en polyneuritis zijn kenmerken van een natuurlijke rubella-infectie in verband gebracht en variëren in ernst en frequentie met leeftijd en geslacht, het hoogst bij volwassen vrouwen en het laagst bij kinderen voor de puberteit.

Chronische artritis is met een natuurlijke rubella-infectie in verband gebracht en aan een uit lichaamsweefsels geïsoleerd persisterend virus en/of virusantigeen toegeschreven. Slechts zelden kregen ontvangers van het vaccin chronische gewrichtsklachten.

Gewrichtssymptomen na vaccinatie bij kinderen zijn zeldzaam en over het algemeen van korte duur. Bij vrouwen ligt de frequentie van artritis en artralgie over het algemeen hoger dan die bij kinderen (kinderen: 0,3 %; vrouwen 12-20 %) en hebben de reacties de neiging meer uitgesproken te zijn en langer te duren. De symptomen kunnen maandenlang en in zeldzame gevallen jarenlang blijven bestaan. Bij adolescente meisjes blijkt de frequentie van de bijwerkingen te liggen tussen die bij kinderen en bij volwassen vrouwen. Zelfs door oudere vrouwen (35-45 jaar) worden deze verschijnselen over het algemeen goed verdragen en zijn ze zelden van invloed op de normale werkzaamheden. Dergelijke reacties komen minder vaak na hervaccinatie dan na

primovaccinatie voor.

4.9. Overdosering

Er zijn geen gegevens bekend met betrekking tot overdosering.

5 FARMACOLOGISCHE EIGENSCHAPPEN

Klinisch onderzoek in 279 drievoudig seronegatieve kinderen tussen de 11 maanden en zeven jaar oud heeft aangetoond dat 'M-M-R' II zeer immunogeen is en over het algemeen goed wordt verdragen. In deze onderzoeken produceerde een eenmalige injectie van het vaccin hemagglutinatieremmende (HAR) antistoffen tegen mazelen bij 95%, neutraliserende antistoffen tegen bof bij 96% en HAR-antistoffen tegen rubella bij 99% van de vatbare patiëntjes. De RA 27/3-rubellastam in 'M-M-R' II geeft direct na vaccinatie hogere concentraties van HAR, complementfixerende en neutraliserende antistoftiters dan andere rubella-vaccinstammen en blijkt een grotere reeks circulerende antistoffen te produceren, waaronder antithèta- en antijota-inducerende antistoffen. De RA 27/3-rubellastam simuleert de natuurlijke infectie immunologisch beter dan andere rubellavaccinvirussen.

De hogere concentraties en de grotere reeks antistoffen na vaccinatie met de RA 27/3-stam van het rubellavirusvaccin blijken te correleren met een grotere weerstand tegen subklinische herinfectie met het natuurlijke virus[11], en een groter vertrouwen op een blijvende immuniteit te geven.

De door het vaccin opgewekte antistoftiters bleken ten minste elf jaar te blijven bestaan zonder aanzienlijke daling.

6 FARMACEUTISCHE GEGEVENS

6.1 Lijst van hulpstoffen

Neomycine, water voor injecties. Het produkt bevat geen conserveermiddel. Sorbitol en gehydrolyseerd gelatine zijn als stabilisatoren toegevoegd.

6.2 Gevallen van onverenigbaarheden

Voor elke injectie en/of oplossing van het vaccin dient een steriele spuit te worden gebruikt die vrij is van conserveermiddelen, antiseptica en detergentia, daar deze stoffen het levend-virusvaccin kunnen inactiveren.
Immuunglobuline niet samen met 'M-M-R' II toedienen.

6.3 Houdbaarheid

De uiterste gebruiksdatum staat op de verpakking (maand, gevolgd door jaar).

Aanbevolen wordt het vaccin zo spoedig mogelijk na reconstitutie te gebruiken.
Na reconstitutie moet het vaccin vernietigd worden als het niet binnen acht uur wordt opgebruikt.

6.4 Speciale voorzorgmaatregelen bij opslag

'M-M-R' II dient voor en na reconstitutie bij 2-8 °C te worden bewaard, buiten invloed van het licht.

'M-M-R II' behoudt tenminste acht maal de minimaal immuniserende dosering, zelfs na 6 weken bij 22 °C of 1 week bij 37 °C. Opslag bij temperatuur buiten 2- 8 °C kan niet aanbevolen worden vanwege moeilijkheden bij het bijhouden van de juiste temperatuur en het bijhouden van herhaalde blootstelling aan temperaturen buiten de koelkast.

Gedurende vervoer dient, om er zeker van te zijn dat geen verlies aan potentie optreedt, de temperatuur beneden 10 °C gehouden te worden.

6.5 Aard en inhoud van de verpakking

Niet van toepassing

6.6 Gebruiksaanwijzing/verwerkingsinstructies

Zie boven.

6.7 Naam en permanent adres van de houder van de vergunning voor het in de handel brengen

MERCK SHARP & DOHME B.V.
postbus 581
2003 PC Haarlem
023-153153

7 NUMMER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

A12

[redacted]

8 DATUM VAN GOEDKEURING/HERZIENING VAN DE SAMENSTELLING

maart 1993.

Extension Directives 89/342 and 89/381 EEC

M-M-R®II

Measles, Mumps and Rubella Vaccine, Live, MSD

Expert Report on the

Chemical, Pharmaceutical and Biological Documentation

By [redacted].....

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Merck Research Laboratories
West Point, Pennsylvania, 19486, USA

July 28, 1992

1. PRODUCT PROFILE

a) Type of application

The application is for the relicensing, under the implementation of Extension Directives 89/342 EEC and 89/381 EEC, of a product which is already licensed and on the market in the member state where this application is made.

b) Chemical and pharmacokinetic properties

The vaccine is a triple antigen containing (1) **ATTENUVAX®** (Measles Virus Vaccine, Live), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo; (2) **MUMPSVAX®** (Mumps Virus Vaccine, Live), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) **MERUVAX®II** (Rubella Virus Vaccine, Live), the Wistar RA27/3 strain of live attenuated rubella virus grown in human diploid cell (WI 38) culture. Pharmacokinetic studies have not been conducted on the live virus vaccine, which is administered subcutaneously.

c) Indications

For simultaneous immunization against measles, mumps and rubella in persons 15 months of age and older.

d) Precautions

Adequate treatment provisions, including adrenalin, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur. Due caution should be employed in administration of M-M-R®II in persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevations which may occur following vaccination.

Children and young adults who are known to be infected with human immunodeficiency viruses but without clinical manifestations of immunosuppression may be vaccinated; however the vaccinees should be monitored closely for vaccinee-preventable diseases because immunization may be less effective than for uninfected persons.

Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of human immune serum globulin.

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has

occurred in the majority of susceptible individuals 7-28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.

There are no reports of transmission of the live measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R®II. Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine; no studies have been reported to date of the effect of live measles virus vaccines on untreated tuberculous children. As for any vaccine, vaccination with M-M-R®II may not result in seroconversion in 100% of susceptible persons given the vaccine.

Pregnancy

Animal reproduction studies have not been conducted with M-M-R®II. It is also not known whether M-M-R®II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination.

Nursing mothers

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating post-partum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Caution should be exercised when M-M-R®II is administered to a nursing woman.

e) Marketing/post-marketing

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M-M-R®II was first licensed in the United States of America on September 15, 1978, and is now licensed generally, worldwide. During this period over [redacted] doses of this vaccine have been supplied worldwide.

2. EXPERT OPINION

Composition and introduction

M-M-R®II vaccine is a sterile lyophilized preparation of (1) **ATTENUVAX®** (Measles Virus Vaccine, Live), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo; (2) **MUMPSVAX®** (Mumps Virus Vaccine, Live), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) **MERUVAX®II** (Rubella Virus Vaccine, Live), the Wistar RA27/3 strain of live attenuated rubella virus grown in human diploid cell (WI 38) culture. The vaccine viruses are the same as those used in the manufacture of the monovalent measles, mumps and rubella vaccines and are mixed prior to being lyophilized. The vaccine contains no preservative.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed in the product literature, the dose for injection is 0.5 mL and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of the United States Reference Measles Virus; 20,000 $TCID_{50}$ of the United States Reference Mumps Virus; and 1,000 $TCID_{50}$ of the United States Reference Rubella Virus. Each dose contains approximately [redacted] of neomycin. Sorbitol and hydrolyzed gelatin are added as stabilizers.

Development Pharmaceutics

The trivalent vaccine was developed by combining three licensed monovalent vaccines. The original formulation of measles, mumps and rubella vaccine, with the tradename M-M-R®, was first licensed for marketing in the United States of America on April 22, 1971. This formulation contained the HPV/77 strain of live rubella virus, used at that time in the rubella virus vaccine, MERUVAX®. On September 15, 1978, amendments of the United States product licenses, to incorporate the use of the more immunogenic Wistar RA27/3 strain of rubella virus, were approved for these vaccines, which were then renamed M-M-R®II and MERUVAX®, respectively. The revised formulations were immediately placed on the market in the United

The monovalent vaccines were developed as follows:

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ATTENUVAX® (Measles Virus Vaccine, Live)

This vaccine was first licensed in the United States of America on March 21, 1968. Edmonston measles virus seed, labelled [redacted], [redacted] passage vaccine pool, dated April 15, 1959, was received from Dr. [redacted]. Prior to receipt, the virus had the following passage history:

[redacted]

The above seed received the following passages at Merck Sharp & Dohme:

[redacted]

Th[redacted] passage in chick embryo cell culture at [redacted] represents the seed virus for all vaccine lots. Tests as applied to the vaccine were performed with satisfactory results.

This live, attenuated measles vaccine is used in the manufacture of the following mixed virus vaccines:

Measles and Mumps Virus Vaccine, Live
Measles and Rubella Virus Vaccine, Live
Measles, Mumps and Rubella Virus Vaccine, Live

The amount of measles virus in the final lyophilized containers must be no less than the equivalent of 1,000 $TCID_{50}$ of the US standard reference per human dose ($10^{2.3}$/0.1 mL when tested in VERO tissue culture).

MUMPSVAX® (Mumps Virus Vaccine, Live), the Jeryl Lynn (B level) strain.

This vaccine was first licensed in the United States of America on December 28, 1967. The Jeryl Lynn strain of mumps virus was isolated from a throat washing specimen collected on March 20, 1966 from a clinical case of mumps. This isolation was conducted by Dr. [redacted] and co-workers in the Virus and Cell Biology Laboratories at

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Merck Sharp & Dohme Research Laboratories, West Point, Pa. This isolate underwent [redacted] passages in embryonated hen's egg amnion and [redacted] passage in chick embryo tissue culture. The seed virus, labelled [redacted] was received from Dr. [redacted] by Merck Sharp & Dohme and received [redacted] additional passage in chick embryo tissue culture. The master seed virus is a pool of harvests from this [redacted] passage. Seed for the production of vaccine represents no more than [redacted] passages from the master seed level.

This live, attenuated mumps vaccine is used in the manufacture of the following mixed virus vaccines:

Measles and Mumps Virus Vaccine, Live
Rubella and Mumps Virus Vaccine, Live
Measles, Mumps and Rubella Virus Vaccine, Live

The amount of mumps virus in the final lyophilized containers must be no less than the equivalent of 20,000 $TCID_{50}$ of the US standard reference per human dose ($10^{3.6}$/0.1 mL when tested in VERO tissue culture).

MERUVAX®II (Rubella Virus Vaccine, Live), Wistar RA27/3 strain

The initial rubella virus vaccine, was first licensed by Merck Sharp & Dohme in the United States of America on June 9, 1969 This vaccine contained the HPV/77 strain of rubella virus. The current rubella virus vaccine containing the Wistar RA-27/3 strain of rubella virus was first licensed in the United States of America on September 18, 1978.

The Wistar RA-27/3 strain of rubella virus was isolated in 1964 by Dr. [redacted] and his co-workers from an explant of a surgically aborted foetus by direct inoculation into WI-38 human diploid fibroblasts. These investigators attenuated this strain by low temperature passage and cloning in WI-38 cell culture. Following receipt of the [redacted] serial passage from Dr. [redacted], additional passages in monitored WI-38 cultures were made by Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania. The master seed is a pool of harvests from the [redacted] passage. Seed for the production of vaccine represents no more than five passages from the master seed level described above.

This live, attenuated rubella vaccine is used in the manufacture of the following mixed virus vaccines:

Measles and Rubella Virus Vaccine, Live
Rubella and Mumps Virus Vaccine, Live
Measles, Mumps and Rubella Virus Vaccine, Live

The amount of rubella virus in the final lyophilized containers must be no less than the equivalent of 1,000 $TCID_{50}$ of the US standard reference per human dose ($10^{2.5}$/0.1 mL when tested in VERO tissue culture).

Manufacture

Cell cultures to provide the host for replication of the viruses include primary chick embryo for measles and mumps and the diploid cell line WI-38 for rubella virus. The cultures are grown as monolayers of cells which are adequately nourished with specific media consisting of amino acids, vitamins and intermediate metabolites which support limited growth and reproduction of the cells. During the early stages a relatively high concentration ( ) of fetal bovine serum is utilized to initiate and promote cell growth. Once the cell sheet is established the growth medium is replaced by a maintenance medium with a lower concentration) of fetal bovine serum to hold the cells until the optimum time for infecting with virus. When the cells have been infected with virus and the harvest procedure commences, the cell sheet is rinsed with a balanced salt solution or basic medium to remove all serum components. An adequate maintenance medium and stabilizer are added. Upon completion of sterility and potency testing of the daily harvests, those which are satisfactory are pooled and filtered to remove cells and cellular debris. Aliquot samples of the bulk pool are removed for testing and the bulk pool sub-divided and filled into sterile canisters for storage at
Following satisfactory completion of all prescribed tests, and release by the regulatory agency is received, the bulk may be used to prepare filled vaccine -- either monovalent or combined, e.g., M-M-R®II.

Each batch of bulk trivalent M-M-R®II vaccine is prepared by aseptically combining aliquots of the three monovalent components with phosphate buffer and stabilizer solution so as to yield upon lyophilization, 1,000 $TCID_{50}$ (tissue culture infectious doses) measles virus, 20,000 $TCID_{50}$ mumps virus, and 1,000 $TCID_{50}$ rubella virus in each dose. The targeted total volume of is sufficient to fill approximately single-dose vials in a single unit lyophilization cabinet.

The vaccine is filled into pre-sterilized vials under Class [redacted] laminar airflow in a filling room meeting Class [redacted] requirements at rest. The air space, no greater than [redacted] from the filling needles is monitored for airborne particulates continuously during filling. The room is monitored for airborne particulates weekly.

The vials are frozen and transferred to the pre-sanitized lyophilization chamber where the temperature is lowered to [redacted] and held until the product temperature reaches a maximum of [redacted]. The vacuum is reduced to [redacted] and held for [redacted] The shelf-temperature is then gradually increased at a rate of [redacted] until the product temperature reaches at leas[redacted] when the product is held in the cabinet for at least [redacted]. Vacuum and product temperature must remain constant for [redacted] before the cycle is regarded as complete. The full cycle takes at least [redacted]. At the end of the cycle, sterile [redacted] is introduced into the chamber to a pressure of about [redacted], and the stoppers are fully inserted by the action of the chamber platen. The sealed vials are removed from the chamber and [redacted] caps applied.

All sterilizing procedures used for solutions, machinery and components, methods of manufacture and lyophilization, have been validated by standard methods and are periodically revalidated in accordance with good manufacturing practices.

In-process control tests for sterility and neomycin content are carried out on the bulk triple vaccine. During filling, the volume level in vials is confirmed in [redacted] along with inspection after lyophilization. Volume of fill: [redacted] (target [redacted]).

Control of starting materials

Stock seed cultures, prepared media and ingredients of media are adequately tested for compliance with in-house or compendial specifications as described in full detail in Part IIC of the application.

Where materials of bovine origin are involved, such as fetal calf serum, confirmation has been obtained from vendors that such materials are derived from herds known to free from virus causing bovine spongiform encephalitis. Similarly, human albumin used in media is confirmed to be free from human immunodeficiency virus by PCR assay.

Control of Bulk Monovalent Vaccine Components

The bulk monovalent measles, mumps and rubella live virus vaccines are adequately tested as follows:

Bulk measles live virus vaccine

Control cells are tested for hemadsorption
A control pool is tested for adventitious agents (in [redacted] avian leukosis and mycoplasma.

The virus harvest is tested for sterility and potency.
The preclarified bulk is tested for adventitious agents (in [redacted] sterility and mycoplasma.
The final bulk is tested for identity, intact cells, sterility, protein nitrogen and potency.

Bulk mumps live virus vaccine

Control cells are tested for hemadsorption
A control pool is tested for adventitious agents (in [redacted]y), avian leukosis and mycoplasma.

The virus harvest is tested for sterility and potency.
The preclarified bulk is tested for adventitious agents (in [redacted], sterility and mycoplasma.
The final bulk is tested for identity, intact cells, sterility, protein nitrogen and potency.

Bulk rubella live virus vaccine

The manufacturer's working cell bank is tested for absence of adventitious agents in [redacted]. The cell bank is further characterized to demonstrate sex, number of chromosomes and chromosome morphology.

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A13
B

Control cells are tested for hemadsorption
A control pool is tested for adventitious agents (in [redacted]), and mycoplasma.

The virus harvest is tested for sterility and potency.
The preclarified bulk is tested for adventitious agents (in [redacted]), sterility and mycoplasma.
The final bulk is tested for identity, intact cells, sterility, protein nitrogen and potency.

Control of the finished product, M-M-R®II trivalent vaccine

The filled trivalent vaccine is adequately tested for:

identity
moisture (max. [redacted])
sterility
safety (complies with the EP Test for Abnormal Toxicity)

potency;	measles	1,000 $TCID_{50}$
	mumps	20,000 $TCID_{50}$
	rubella	1,000 $TCID_{50}$

Stability

Frozen bulk vaccines

Due to the thermolabile nature of the vaccines, all steps in the manufacture procedure for bulk and final product are conducted as rapidly as possible to insure integrity and stability of the product. Upon completion of the pooling operations aliquots of the bulk pool for each virus are rapidly frozen and immediately transferred to refrigerated vaults where the temperature is maintained at less than [redacted].

Stability of the finished product

When shipped at [redacted] or below, the lyophilized vaccine is stable for at least 24 months. Although most facilities store the lyophilized vaccine in the temperature range of 2 to 8°C, (36 to 46°F) which is normal for most refrigerators, the lyophilized vaccine may be stored at temperatures below [redacted] with no effect on potency.

Virus in the reconstituted vaccine is subject to degradation by light as well as temperature and, therefore, it is recommended that the reconstituted vaccine be stored in a dark place at 2 to 8°C. Although potency of the vaccine is retained for more than 24 hours at 2 to 8°C after reconstitution, it is recommended that the reconstituted vaccine be discarded after 8 hours at 2 to 8°C, since neither the lyophilized vaccine nor the sterile diluent contain a preservative.

Clinical studies showing dose response of vaccinees were considered in establishing surplus potency to compensate for incomplete real-time stability data. The dose response studies showed the minimum effective dosage for each virus strain to be:

	$TCID_{50}$/dose
Measles virus	40
Mumps virus	317
Rubella virus	3

Current regulations worldwide now call for establishment of firm parameters for determination of expiry of each product. However, the wisdom of the decision to allow initial introduction of measles, mumps and rubella to combat epidemic disease resulted in saving of countless lives with nearly complete eradication of disease in areas where universal use of the vaccines was possible.

Throughout the years stability studies measuring retention of virus infectivity for each vaccine have continued on all formulations -- both monovalent and multivalent. Each vaccine shares a comparable formulation of buffer and stabilizer system resulting in ability to compare virus stability in both monovalent and multivalent formulations. The data reported section IIF provide a summary of stability tests performed on the various formulations, as well as a review of the results of real-time

Stability of Vaccine at Elevated Temperatures

When subjected to temperatures above the required storage temperature range, the lyophilized vaccines in both monovalent and multivalent form degrade more rapidly than vaccine which has been properly stored.

Although a reduction of approximately [redacted] as seen after [redacted] at [redacted] for both measles virus and mumps virus still results in vaccine potency in excess of the minimum effective dose, the data nevertheless demonstrate the adverse effects of elevated temperature and emphasize the need for proper shipping and storage procedures.

Stability of Reconstituted Vaccine

A summary of the data from studies of the stability of reconstituted vaccine is seen in Table 2.2.3. In these studies samples of monovalent and multivalent vaccine were restored with the proper volume of diluent as prescribed for inoculation of vaccinees and stored at 2-8°C, which is the recommended storage temperature range for all Merck live virus vaccines. At intervals of [redacted] restoration, samples were inoculated into susceptible cell culture systems used for determination of potency and the amount of residual infectious virus was determined. Linear regression analyses were performed on the mean potency values found at each time interval with the resultant slopes averaged to determine potency loss.

Stability of Reconstituted Measles Virus, Mumps Virus and Rubella Virus at 2-8°C for [redacted]

	Average Loss [redacted]	Standard Deviation [redacted]
Measles (n = [redacted]		
Mumps (n = [redacted]		
Rubella (n = [redacted]		

Although immunizing levels of infectious virus of each strain remains in suspension after [redacted] at 2-8°C, discard of the reconstituted vaccine is recommended because of the absence of a preservative.

Other Information

Full information is provided on the details of the manufacturing facilities for M-M-R®II, including buildings and facilities, floor plans, animal facilities, equipment, labelling of products, retention of samples, organization of responsible personnel which confirms that the facilities are fully adequate for production of vaccines according to good manufacturing practice.

Conclusions

The information provided in Part II of the documentation, together with widespread and extensive clinical experience over 14 years has shown that M-M-R®II is consistently produced as an effective and well tolerated vaccine.

3. SUMMARY TABLES OF THE DATA PRESENTED

PART IIA: COMPOSITION Pages IIA-1 to IIA-15

Description. Page IIA-1

M-M-R®II vaccine is a sterile lyophilized preparation of (1) **ATTENUVAX®** (Measles Virus Vaccine, Live), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo; (2) **MUMPSVAX®** (Mumps Virus Vaccine, Live), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) **MERUVAX®II** (Rubella Virus Vaccine, Live), the Wistar RA27/3 strain of live attenuated rubella virus grown in human diploid cell (WI 38) culture.

Composition of the lyophilized vaccine. Page IIA-2

In each dose:

Measles virus	1,000 $TCID_{50}$
Mumps virus	20,000 $TCID_{50}$
Rubella virus	1,000 $TCID_{50}$

Other ingredients:

Sodium phosphate monobasic	Reagent, ACS
Sodium phosphate dibasic	Reagent, ACS
Sodium bicarbonate	Reagent, ACS
Medium 199	
Minimum Essential Medium, Eagle	
Neomycin	USP
Phenol red	
Albumin, human	USP
Sorbitol	USP/NF
Potassium phosphate, monobasic	Reagent, ACS
Potassium phosphate, dibasic	Reagent, ACS
Gelatin, hydrolyzed	
Sucrose	Reagent, ACS
Monosodium L-glutamate	

[redacted]

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Diluent **Page IIA-3**

The lyophilized vaccine is accompanied by a sterile diluent which contains no ingredient. The composition is as follows

Water for Injection in Bulk EP	0.5 mL

Containers **Page IIA-4**

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The lyophilized vaccine is contained in nomina clear type I tubing glass vials with necks having an finish. The vial is closed by a butyl stopper and capped with an with a dark blue .

The diluent is contained in nominal clear type I tubing glass vials with necks having an finish. The vial is closed by a butyl stopper and capped with an with a grey .

Clinical Trial Formula **Page IIA-4**

The formulation described above for the marketing vaccine was used in the clinical trials.

Development Pharmaceutics **Page IIA-5**

The trivalent vaccine was developed by combining three licensed monovalent vaccines. The original formulation of measles, mumps and rubella vaccine, with the tradename M-M-R®, was first licensed for marketing in the United States of America on April 22, 1971. This formulation contained the HPV/77 strain of live rubella virus, used at that time in the rubella virus vaccine, MERUVAX®. On September 15, 1978, amendments of the United States product licenses, to incorporate the use of the more immunogenic Wistar RA27/3 strain of rubella virus, were approved for these vaccines, which were then renamed M-M-R®II and MERUVAX®, respectively. The revised formulations were immediately placed on the market in the United States.

ATTENUVAX® (Measles Virus Vaccine Live, MSD)

This vaccine was first licensed in the United States of America on November 26, 1968.

Edmonston measles virus seed, labelled [redacted] passage vaccine pool, dated April 15, 1959, was received from Dr. [redacted] Prior to receipt, the virus had the following passage history:

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[redacted]

The above seed received the following passages at Merck Sharp & Dohme:

[redacted]

The [redacted] passage in chick embryo cell culture at [redacted] represents the seed virus for all vaccine lots. Tests as applied to the vaccine were performed with satisfactory results.

This live attenuated measles vaccine is used in the manufacture of the following combined virus vaccines:

Measles and Mumps Virus Vaccine Live
Measles and Rubella Virus Vaccine Live
Measles, Mumps and Rubella Virus Vaccine Live

The amount of measles virus in the final lyophilized containers must be no less than the equivalent of 1,000 $TCID_{50}$ of the US standard reference per human dose ($10^{2.3}$/0.1 mL when tested in VERO tissue culture).

MUMPSVAX® (Mumps Virus Vaccine Live, MSD)

This vaccine was first licensed in the United States of America on December 28, 1967.The Jeryl Lynn strain of mumps virus was isolated from a throat washing specimen collected on March 20, 1966 from a

clinical case of mumps. This isolation was conducted by Dr. [redacted] and co-workers in the Virus and Cell Biology Laboratories at Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania, U.S.A. This isolate underwent [redacted] passages in embryonated hen's egg amnion and one passage in chick embryo fibroblast (CEF) tissue culture. The seed virus, labeled [redacted], was received from Dr. [redacted] by Merck Sharp & Dohme and received [redacted] additional passage in chick embryo tissue culture. The master seed virus is a pool of harvests from thi[redacted] passage. Seed for the production of vaccine represents no more than [redacted] passages from the master seed level.

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This live attenuated mumps vaccine is used in the manufacture of the following combined virus vaccines:

Measles and Mumps Virus Vaccine Live
Rubella and Mumps Virus Vaccine Live
Measles, Mumps and Rubella Virus Vaccine Live

The amount of mumps virus in the final lyophilized containers must be no less than the equivalent of 20,000 $TCID_{50}$ of the US standard reference per human dose ($10^{3.0}$/0.1 mL when tested in VERO tissue culture).

MERUVAX®II (Rubella Virus Vaccine Live, MSD)

The initial rubella virus vaccine, was first licensed by Merck Sharp & Dohme in the United States of America on June 9, 1969. This vaccine contained the HPV/77 strain of rubella virus.

The current rubella virus vaccine containing the Wistar RA 27/3 strain of rubella virus was first licensed in the United States of America on September 15, 1978. The Wistar RA 27/3 strain of live attenuated rubella virus, grown in human diploid cell (WI-38) culture, was selected to replace the HPV/77 strain because it elicits higher immediate post-vaccination HI, complement-fixing and neutralizing antibody levels than other strains of rubella vaccine. It has also been shown to induce a broader profile of circulating antibodies including anti-theta and anti-iota precipitating antibodies. The RA 27/3 strain immunologically simulates natural infection more closely than other rubella vaccine viruses. The increased levels and broader profile of antibodies produced by the RA 27/3strain rubella virus vaccine appear to correlate with greater resistance to

sub-clinical reinfection with the wild virus and provide greater confidence for lasting immunity.

The Wistar RA 27/3 strain of rubella virus was isolated in 1964 by Dr. [redacted] and his co-workers from an explant of a surgically aborted foetus by direct inoculation into WI-38 human diploid fibroblasts. These investigators attenuated this strain by low temperature passage and cloning in WI-38 cell culture. Following receipt of the [redacted] passage from Dr. [redacted], additional passages in monitored WI-38 cultures were made by Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania. The master seed is a pool of harvests from the [redacted] passage. Seed for the production of vaccine represents no more than [redacted] passages from the master seed level described above.

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This live attenuated rubella vaccine is used in the manufacture of the following combined virus vaccines:

Measles and Rubella Virus Vaccine Live
Rubella and Mumps Virus Vaccine Live
Measles, Mumps and Rubella Virus Vaccine Live

The amount of rubella virus in the final lyophilized containers must be no less than the equivalent of 1,000 $TCID_{50}$ of the US standard reference per human dose ($10^{2.3}$/0.1 mL when tested in RK-13 tissue culture).

PART IIB: METHOD OF PREPARATION Page IIB-1 to IIB-29

Manufacturing formula for the lyophilized vaccine Page IIB-1

Each batch of bulk trivalent M-M-R®II vaccine is prepared by aseptically combining aliquots of the three monovalent components with phosphate buffer and stabilizer solution. They are blended in a sterile receptacle in the proportions given below, so as to yield upon lyophilization, 1,000 $TCID_{50}$ (tissue culture infectious doses) measles virus, 20,000 $TCID_{50}$ mumps virus, and 1,000 $TCID_{50}$ rubella virus in each 0.5 mL dose.

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Bulk multivalent vaccine [redacted]
Buffer
Stabilizer

The targeted total volume of [redacted] is sufficient to fill approximately [redacted] single-dose vials in a single unit lyophilization cabinet.

Manufacture of Bulk Vaccine Page IIB-2

Filing and lyophilization

Each step of manufacturing, filling and testing of the vaccine is carried out by qualified and well-trained personnel. All manufacturing and testing operations as well as all physical facilities meet and fulfill the Good Manufacturing Procedures described in US 21 Code of Federal Regulations and in the EC Guide to Good Manufacturing Practice for Medicinal Products.

Subdivision of the vaccine Page IIB-2

Sterilization of Final Containers

Vials are transferred to a metal tray and washed with distilled water in a washing machine programmed with an automated wash cycle.

The washed vials are sterilized by passing them through a validated dry-heat sterilization tunnel at a rate of [redacted] (dwell time

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of [redacted]) and a temperature of [redacted]. These sterile vials are transferred to the filling area under Class [redacted] clean air. An alternate sterilization method may be used if required. This method consists of sterilizing the washed vials in a dry-heat oven for [redacted], using a validated load pattern.

As expressed in the USP guidelines, depyrogenization is an integral part of a validation study for dry-heat sterilization. Both of the sterilization methods used for the washed vials above reduce the pyrogen level of bacterial endotoxin (as measured by the Limulus assay) more than [redacted] of the original level.

Filling of vaccine vials **Page IIB-3**

Predetermined quantities of monovalent vaccine components contained in separate receptacles are thawed by [redacted]. Dilution of the vaccine and addition of stabilizer is carried out under Class [redacted] laminar flow hoods meeting [redacted] requirements.

Container contents are mixed to insure an homogeneous blending of diluent and vaccine concentrates. The temperature of the batch is held at [redacted] throughout the blending and filling procedure. The vials are filled on an automatic filling machine equipped with sterile components. Instrumentation is calibrated to fill at [redacted] per vial with plus or minus [redacted] tolerance. During filling, the fill volume of [redacted] vials [redacted]) is confirmed on [redacted] tray [redacted] vials per tray).

Vials are filled under Class [redacted] laminar airflow in a filling room meeting Class [redacted] requirements at rest. The air space no greater than [redacted] inches from the filling needles is monitored continuously during filling for airborne particulates employing a Particle Measuring System [redacted]). This same air space is monitored during filling operations for microbial contamination using the [redacted] method (described in Section 2.2.4 below) and the impression plates [redacted]), respectively. In addition, weekly particulate counts are monitored for the room. Filling components such as vials, stoppers, needles and connecting components are sterilized under validated process cycles as discussed elsewhere in this section.

After filling with the appropriate volume of vaccine and buffered stabilizer the trays of vials are mounted on a conveyor which travels through a tunnel containing liquid nitrogen vapor. The vials, whose contents are rapidly frozen, are transferred to the lyophilization cabinet or to a storage freezer from which they are manually loaded into the chamber later as required.

Lyophilization of the vaccine **Page IIB-4**

The vials are frozen and transferred to the pre-sanitized lyophilization chamber where the temperature is lowered to [redacted] and held until the product temperature reaches a maximum of [redacted]. The vacuum is reduced to [redacted] and held for [redacted]. The shelf-temperature is then gradually increased at a rate of [redacted] until the product temperature reaches at least [redacted] when the product is held in the cabinet for at least [redacted]. Vacuum and product temperature must remain constant for [redacted] before the cycle is regarded as complete. The full cycle takes at least [redacted] At the end of the cycle, sterile [redacted] is introduced into the chamber to a pressure of about [redacted] and the stoppers are fully inserted by the action of the chamber platen. The sealed vials are removed from the chamber and [redacted] applied.

In-process testing of the vaccine **Page IIB-5**

In-process control tests for sterility and neomycin content are carried out on the bulk triple vaccine. During filling, the volume level in vials is confirmed in [redacted] along with inspection after lyophilization. Volume of fill: [redacted] (targe[redacted]). Air quality monitoring tests of the filling area are as described. Settle plate testing is not used in the filling or lyo areas. Instead, th[redacted] procedure for microbial testing is used. This method monitors airborne microbial levels by [redacted] As a routine procedure, supplies of vials, stoppers and seals are inspected for correct dimension and for visual defect by Merck Manufacturing Division Supply Inspection Department at the West Point plant.

Validation of vaccine manufacture **Page IIB-6**

All equipment and containers used in the processing of the bulk diluent and bulk vaccine, as well as the bulk and final forms of these components, are sterilized using procedures that have been validated by the Merck Manufacturing Division Validation Department. A description of general administration and operating procedures for live virus vaccine production and control is found in Part II Q.

Validation of lyophilization **Page IIB-6**

The lyophilization process utilized by the Merck Manufacturing Division is common to all formulations of monovalent and multivalent live virus vaccines composed of measles virus, mumps virus and rubella virus. The following sections describe validation procedures and laboratory reports for the sterilization of the lyophilization cabinet and the lyophilization procedure for single dose formulations.

Validation of the SIP for lyophilization cabinet **Page IIB-7**

Objective

The objective of SIP validation is to demonstrate that the sterilization process provides a level of assurance of at least [redacted] probability of microbial survival. A13

Purpose

To outline the testing procedures, methods, and acceptance criteria employed for validation of sterilize-in-place systems.

Procedure

Validation consists of the following types of tests:

Distribution/Penetration Validation Testing

The objective of the distribution/penetration testing is to demonstrate the temperature uniformity within a specified system.

A12
A13

For each distribution/penetration temperature test, a minimum of [redacted] test thermocouples shall be used unless the system has fewer than [redacted] available locations. Prior to and after any temperature monitoring, the temperature recording system shall be calibrated by placing all thermocouples in a temperature reference bath adjusted to the sterilize-in-place systems set point temperature, [redacted]. A certified resistance temperature device (RTD) traceable to the National Bureau of Standards is used to determine the actual reference temperature. When the temperature readings have stabilized, the pre-test difference (maximum [redacted]) between the RTD reading (actual temperature) and the temperature recording printout (recorded temperature) is the correction factor applied to all recorder printouts during the tests.

A post-test calibration is used as a thermocouple operation check only. The temperature data from any thermocouple not recording within [redacted] of the reference temperature during the post-test calibration will not be used. For the purpose of monitoring the drift of the temperature recorder, an [redacted] will be employed. The emf recorded shall normally not drift greater than [redacted] during the test.

Microbial Challenge Validation Testing

The objective of the microbial challenge test is to demonstrate that the steam sterilization process provides a level of assurance of at least [redacted] probability of microbial survival.

Microbial challenge testing consists of locating biological indicators at points within the system or product being sterilized. For each test, a minimum of [redacted] biological indicators shall be used, when locations are available, with a challenge of [redacted] (range [redacted]) spores of [redacted]. Indicators shall be placed adjacent to the specified temperature indicators. Upon completion of microbial challenge test, the spore challenges shall be placed in containers of growth-promoting culture media and incubated at [redacted] for a minimum of [redacted]. Inoculated culture media shall be incubated at [redacted] for a minimum of [redacted].

For each microbial challenge test, [redacted] biological indicator shall be used as a positive control. [redacted] indicator shall not be subjected to the sterilization cycle.

Validation of the Lyophilization Process Page IIB-12 A12

Objective

To demonstrate that the lyophilization process for M-M-R®II consistently yields product which meets MMD and compendial standards, as well as established process capability.

Purpose

To outline the procedure employed for validation of the lyophilization process of M-M-R®II.

Sampling, testing and evaluation

The validation testing plan will involve expanded testing of lyophilized vial samples. Expanded validation testing will be in addition to normal release testing performed on the product. The study will include three consecutive satisfactory lots of M-M-R®II.

Lyophilized vial samples will be taken from [redacted] specified locations throughout the lyo chamber. The samples will be tested and evaluated as specified in the product specific Quality Standard Manual. The lyophilized vial sampling plan is provided below:

Lyophilized vial sampling plan

Test	Location numbers	No of vials per location	Total No. of vials
[redacted]			

The product and shelf temperature data, as well as chamber pressure data will be plotted and compared to lyophilization cycle parameters for M-M-R®II.

For information purposes only, the reject percentages determined by 100% inspection will be evaluated. Reject percentages that may be influence by the lyophilization process (i.e. bad lyo plug quality) will be compared to historical reject percentages of the same type.

Routine Examinations

The vials, stoppers and caps used for both lyophilized vaccine and diluent are sampled upon receipt from the manufacturer according to statistically validated methods and tested for correct appearance, mass dimensions, cleanliness and absence of defective items. Glass vials are checked also for conformity with compendial requirements for Type 1 glass.

Specifications

Glass Vial

A [redacted], round, [redacted] Type 1 flint glass tubing vial is used for single dose vaccine. The features and dimensions of the vial (Merck Manufacturing Division Code No. [redacted] are given.

Stopper

The [redacted] stopper used for the single dose vial is the [redacted] grey butyl lyophilization stopper. The features and dimensions for this stopper (Merck Manufacturing Division Code No. [redacted] are given in Figure 3.2.2.1.2. The composition of the butyl stopper is proprietary information of [redacted] and may be obtained by regulatory agencies directly from the European licensee whose address is:

[redacted]

Cap and Seal

The cap and seal for the single dose vaccine vial is a [redacted] with a dark blue [redacted] cap. It is [redacted] on the outside.

Diluent

The diluent for the vaccine is supplied in vials of Type 1 tubing glass whose features and dimensions are the same as described for comparable vaccine vials. The stoppers for the closure system utilizes [redacted] grey butyl stopper. A14

Raw Materials **Page IIB-27**

Raw Materials Used in the Vaccine

Hanks' Balanced Salt Solution and traditional cell culture media such as Medium 199 and variations of Eagles' Medium are universally used in the propagation of many cell systems used for production of a variety of live and/or inactivated virus vaccines. They are complex mixtures of essential chemicals needed for growth and replication of the cell cultures.

Vaccine Final Bulk

Measles Virus Bulk

The raw materials used in the preparation of the measles virus bulk include:

i) Medium 199 with stabilizer is used in the final stage of vaccine harvest.

ii) Sucrose/Phosphate/Glutamate/Albumin Solution is used as a stabilizer solution and is added at time of pooling. The constituents of this medium are:

25% Albumin (human) USP
Potassium phosphate, monobasic, reagent
Potassium phosphate, dibasic, reagent
Monosodium L-glutamate, monohydrate
Sucrose, crystalline, reagent
Double distilled water

Mumps Virus Bulk

The raw materials used in the preparation of mumps virus bulk include:

i) Medium 199 10 X liquid with stabilizer or Medium 199 powder with stabilizer is used in the final stage of vaccine harvest.

Rubella Virus Bulk

The raw materials used in the preparation of rubella virus bulk include:

i) Eagles Minimum Essential Medium (EMEM) plus human albumin is used in the final phase of vaccine harvest.

ii) A Sorbitol and Gelatin Stabilizer is used as a virus stabilizer and is added at time of freezing of virus harvests. The constituents of this medium include:

Gelatin, processed/water soluble
Sorbitol, NF
Double distilled water

Buffer

i) Sodium phosphate buffer is used to provide buffering capacity and is added at pooling immediately prior to filling operation. The constituents of this medium are:

Sodium phosphate, dibasic, reagent
Sodium phosphate, monobasic, reagent
Double distilled water

Stabilizer

i) GOS Stabilizer is added to the final bulk vaccine to adjust overall stabilizer content of the vaccine.

The constituents of this medium include:

Gelatin, Processed/Water Soluble
Sorbitol, NF
Double Distilled Water
Medium 199, 10X concentrate
Sodium Bicarbonate, Reagent, ACS
Phenol Red

[redacted]

PART IIC: CONTROL OF STARTING MATERIALS

Active Ingredient **Page IIC-1**

Specifications and routine tests **Page IIC-1**

Specifications for the Bulk Vaccine

After blending the bulk vaccine, aliquots are removed aseptically for testing. The thermolabile nature of the product requires that filling proceed immediately.

The multivalent bulk vaccine is tested against the following specifications:

Sterility: Meets the requirements of EP, USP and 21CFR 610.12

Neomycin: Limit: [redacted] A6

Test methods and validation **Page IIC-1**

Sterility

The sterility of the multivalent bulk is tested by standard pharmacopoeia procedures.

Neomycin

This procedure is designed to test products for neomycin potency using an agar diffusion assay to demonstrate the ability of the antibiotic to kill or inhibit the growth of the test organism, Staphylococcus epidermidis, which is sensitive to neomycin. The determination of potency is based on comparison of zones of inhibition produced by a standard solution with those produced by the test sample. All assay plates are treated with both the standard and the test solutions so that both are subjected to the same conditions.

SCIENTIFIC DATA Page IIC-2

Nomenclature Page IIC-2

Generic name: Measles, Mumps and Rubella Virus Vaccine, Live

Trade name: M-M-R®II

Description Page IIC-2

The active ingredients of the lyophilized vaccine are:

1. Measles virus - a more attenuated strain derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo
2. Mumps virus - the Jeryl Lynn (B level) strain grown in cell cultures of chick embryo
3. Rubella virus - the Wistar RA 27/3 strain grown in human diploid cell (WI-38) culture

Manufacture Page IIC-2

Cell cultures to provide the host for replication of the viruses include primary chick embryo for measles and mumps and the diploid cell line WI-38 for rubella virus. The cultures are grown as monolayers of cells which are adequately nourished with specific media consisting of amino acids, vitamins and intermediate metabolites which support limited growth and reproduction of the cells. During the early stages a relatively high concentration [redacted]) of fetal bovine serum is utilized to initiate and promote cell growth. Once the cell sheet is established the growth medium is replaced by a maintenance medium with a lower concentration [redacted]) of fetal bovine serum to hold the cells until the optimum time for infecting with virus. When the cells have been infected with virus and the harvest procedure commences, the cell sheet is rinsed with a balanced salt solution or basic medium to remove all serum components. An adequate maintenance medium and stabilizer are added.

A2

Upon completion of sterility and potency testing of the daily harvests, those which are satisfactory are pooled and filtered to remove cells and cellular debris. Aliquot samples of the bulk pool are removed for testing

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A14

and the bulk pool sub-divided and filled into sterile canisters for storage at [redacted]

Following satisfactory completion of all prescribed tests, and release by the regulatory agency is received, the bulk may be used to prepare filled vaccine -- either monovalent or combined, e.g., M-M-R®II.

Manufacturing Source **Page IIC-4**

The manufacture of individual bulk vaccines and filling of M-M-R®II will be carried out by:

[redacted]

A detailed description of the live virus vaccine manufacturing facilities and general administration procedures is found in Part II Q.

Manufacture of measles virus bulk **Page IIC-4**

A flowchart which provides an outline of the manufacturing steps for measles virus bulk is seen in Table 1.2.3.2.1.

Manufacture of mumps virus bulk **Page IIC-12**

A flowchart which provides an outline of the manufacturing steps for mumps virus bulk is seen in Table 1.2.3.2.2.

Manufacture of rubella virus bulk **Page IIC-19**

A flowchart which provides an outline of the manufacturing steps for rubella virus bulk is seen in Table 1.2.3.2.3.

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ATTENUVAX®
Measles Virus Vaccine Live, MSD
Flow Chart for Manufacturing and Control - Bulk
Refer to Part II C
BULK PRODUCT

MANUFACTURING PROCESS (Section 1.2.3)				CONTROL TESTING (Section 1.2.4)	
		Culture System			
Time	Step in Process	Control	Vaccine	Control	Vaccine
(Day)					
[redacted]	Prepare seed virus		2.1.1		
	Prepare cells	2.1.2	2.1.2		
	Plant cells	2.1.3	2.1.3		
	Incubate				
	Refeed	2.1.4.i			
	Refeed - add virus		2.1.4.ii		
	Rinse and refeed	2.1.4.iii	2.1.4.iii		
	Harvest and refeed	2.1.4.iv	2.1.4.iv		
	Store harvests	2.1.4.iv	2.1.4.iv		
	Control pool	2.1.4.v		1.1	
	Bulk pool		2.1.4.v		
	- pre-clarified				1.2
	- final bulk				1.3
	- dispensed				1.3

Upon successfull completion of all testing, a release protocol and aliquoted samples are sent to U.S. Center for Biologics Evaluation and Research (CBER). Filling operations begin only after receipt of written release from CBER.

[redacted]

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MUMPSVAX®
Mumps Virus Vaccine Live, MSD
Flow Chart for Manufacturing and Control - Bulk
Refer to Part II C

BULK PRODUCT

MANUFACTURING PROCESS (Section 1.2.3)				CONTROL TESTING (Section 1.2.4)	
		Culture System			
Time	Step in Process	Control	Vaccine	Control	Vaccine
(Day)					
[redacted]	Prepare seed		2.2.1		
	Prepare cells	2.2.2	2.2.2		
	Plant cells	2.2.3	2.2.3		
	Rinse and refeed	2.2.4.i			
	Rinse, refeed, add virus		2.2.4.ii		
	Refeed	2.2.4.iii			
	Refeed and harvest		2.2.4.iii		
	Store harvests	2.2.4.iii	2.2.4.iii		
	Control pool	2.2.4.iv		2.1	
	Bulk pool		2.2.4.iv		2.2
	pre-clarified				2.2
	final				2.3

Upon successful completion of all testing, a release protocol and aliquoted samples are sent to U.S. Center for Biologics Evaluation and Research (CBER). Filling operations begin only after receipt of written release from CBER.

[redacted]/1

MERUVAX®II
Rubella Virus Vaccine Live, MSD
Flow Chart for Manufacturing and Control - Bulk
Refer to Part II C

A2

MANUFACTURING PROCESS (Section 1.2.3)		BULK PRODUCT Culture System		CONTROL TESTING (Section 1.2.4)	
Time	Step in Process	Control	Vaccine	Control	Vaccine
(Day)					
[redacted]	Prepare seed virus		2.3.1		
	Manufacture Work Cell Bank-PDL 21-23	2.3.2		3.1	
	Prepare cells	2.3.3			
	Plant cells and incubate	2.3.3			
	Sub-culture				
	-1	2.3.3			
	-2	2.3.3			
	-3	2.3.3			
	Refeed	2.3.4.i			
	Refeed and add virus		2.3.4.ii		
	Rinse and refeed	2.3.4.iii	2.3.4.iii		
	Harvest and refeed ([redacted] intervals)	2.3.5.i	2.3.5.ii		
	Store harvests	2.3.5.i	2.3.5.ii		
	Control Pool	2.3.6.ii		2.3	
	Bulk pool		2.3.6.i		3.3
	- pre-clarified		2.3.6.i		3.3
	- final		2.3.6.i		3.3
	- dispensed				

Upon successful completion of all testing, a release protocol and aliquoted samples are sent to U.S. Center for Biologics Evaluation and Research (CBER). Filling operations begin only after receipt of written release from CBER.

[redacted]

A3a

The preclarified bulk is tested for adventitious agents (in [redacted]), sterility and mycoplasma.

The final bulk is tested for identity, intact cells, sterility, protein nitrogen and potency.

Rubella virus bulk **Page IIC-54**

The manufacturer's working cell bank is tested for absence of adventitious agents in [redacted]. The cell bank is further characterized to demonstrate sex, number of chromosomes and chromosome morphology.

Control cells are tested for hemadsorption

A control pool is tested for adventitious agents (in [redacted]), and mycoplasma.

The virus harvest is tested for sterility and potency.

The preclarified bulk is tested for adventitious agents (in [redacted]), sterility and mycoplasma.

The final bulk is tested for identity, intact cells, sterility, protein nitrogen and potency.

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Other ingredients used in manufacture Page IIC-73

Measles Virus Bulk Vaccine

Name	Product Number	Use
Medium 199	[redacted]	Basic cell culture Medium
0.25% Trypsin Sol.		Enzyme solution used to prepare cell suspensions
Fetal Bovine Serum, Irradiated		Serum supplement to promote cell growth
Medium 199 with 2% Fetal Bovine Serum		Cell maintenance medium
Hanks' Balanced Salt Solution		Rinse medium

Mumps Virus Bulk Vaccine

Name	Product Number	Use
Medium 199	[redacted]	Basic Cell Culture Medium
0.25% Trypsin		Enzyme solution used to prepare cell suspensions.
Fetal Bovine Serum, Irradiated		Serum supplement to support cell growth.
Hanks' Balanced Salt Solution		Rinse medium
Medium 199 plus Stabilizer		Maintenance medium for control cells.
Medium 199 plus Stabilizer		Harvest medium

Rubella Virus Bulk Vaccine

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Name	Product Number	Use
Basal Medium Eagle with Earles' Salts	[redacted]	Basic cell culture medium
KCl-Citrate Trypsin		Enzyme solution used to prepare cell suspensions
Fetal Bovine Serum Irradiated		Serum supplement to promote cell growth
Hanks' Balanced Salt Solution		Rinse medium
Minimum Essential Medium with 2% Fetal Bovine Serum		Cell maintenance medium
Minimum Essential Medium with 0.4% Human Serum Albumin		Harvest Medium

25% Albumin (human), USP

The source of human albumin is a 25% solution of human albumin purchased from licensed manufacturers in the United States of America with the primary source of supply being [redacted] The product is released by the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research (CBER). The product meets specifications described in United States Pharmacopoeia XXII. A14

The collection of the human plasma in FDA-licensed facilities and the method of manufacture of batches of product adhere also to regulations in the U.S. Code of Federal Regulations, Part 640.80. Plasma units are obtained from asymptomatic adult donors whose physical examinations and clinical histories are acceptable and whose plasma are tested and found to be negative for HBsAg and negative for anti-HIV-1 antibodies. Pre-acceptance testing of each lot of product by Merck Manufacturing Division calls for the test sample of acceptable lots to be free of the presence of HIV-1 sequences by reverse transcriptase/polymerase chain reaction methodology.

Trypsin

In addition to vendor specifications of freedom from detectable microorganisms and adventitious agents samples from all lots are tested by the Merck Manufacturing Division on a pre-acceptance basis and released by the Biological Quality Control Laboratories. Samples in the pre-acceptance test must show freedom from microorganisms including yeast, fungi and mycoplasma and freedom from porcine parvovirus. The test for absence of parvovirus is conducted by inoculation of sample into cultures of porcine kidney PSY-15 cell line, which are sensitive to porcine parvovirus. The challenge cell cultures must show freedom from the virus as determined by absence of hemagglutination of guinea pig red blood cells and absence of virus as shown by immunofluorescent microscopy using fluorescein conjugated porcine parvovirus antiserum obtained from the United States Department of Agriculture Animal Plant Health Inspection Services (APHIS).

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Fetal Bovine Serum

In addition to vendor specifications of freedom from detectable microorganisms and adventitious agents samples from all lots are tested by the Merck Manufacturing Division on a pre-acceptance basis, and released by the Biological Quality Control Laboratories. Samples in the pre-acceptance test must show freedom from microorganisms including yeast, fungi and mycoplasma and freedom from viral adventitious agents as determined by:

1. Negative cytopathic effect in [redacted] and [redacted] cell cultures.

2. No hemagglutination or hemadsorption seen in above cell culture systems.

3. No detectable non-cytopathogenic viruses as indicated by fluorescent antibody testing.

All acceptable lots of fetal bovine serum are secured from herds within the continental United States where the presence of bovine spongiform encephalopathy has not been detected.

Packaging materials Page IIC-81

Storage of Bulk Vaccines

Because of the thermolabile nature of the virus constituents of the bulk vaccines processing of each stage of manufacture after harvesting must be performed quickly and at a temperature range compatible with each stage of manufacture.

Upon completion of the liquid bulk pool, aliquots of the bulk vaccine are transferred aseptically into sterile stainless steel vessels in such volume to approximate the quantity of vaccine of each strain needed for one filling operation. The aliquoted vaccine is rapidly frozen and stored under mechanical refrigeration at less than [redacted] When needed for filling an appropriate number of containers are removed from the freezer, transferred to the sterile filling area where the contents of the containers are thawed in preparation for the filling operation.

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Stainless Steel Vessels Used for Storing Frozen Bulk Vaccine

Specifications

The vessel of [redacted] capacity is purchased from [redacted].

Type [redacted] stainless steel is used for all parts of the vessel which will be wetted by the product.

Documentation defining the analysis of composition of the metal is provided by the supplier and the metal is traceable to the "heat" at the steel mill where produced. Because of the importance of molybdenum in resisting corrosion, this element is specified to be at the highest reasonable level within the normal specified range of [redacted] for Type [redacted] stainless steel.

Batch analysis Page IIC-82

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In 1991 Merck Manufacturing Division introduced an updated computer system for tracking and identifying all products as they move through manufacturing and packaging operations. A master formula and manufacturing production record are employed in the manufacture and packaging of the product. This record contains the nomenclature of the product and a product identification number definitive for that product. The identification number may consist of four or five digits depending on when the product was introduced and what division has control of the item. Included also on this original document will be the production formula number (production number, which is a discrete number consisting of five or seven digits which serves to identify the material through all states of compounding, testing and packaging). This number is not shown on finished containers or labels, but the manufacturing history can be traced from this number. In the case of biologicals, this may also be referred to as a bulk number. Aliquots of the bulk may then be combined with other intermediate stages or carried alone in a filling operation. At this point, a second five or seven digit discrete number is used to identify the filling of a biological product. The discrete numbers may or may not be issued in sequence.

Bulk vaccine is not continuously produced in all vaccine production units. Production campaigns are conducted for varying intervals as required to meet demands for vaccine. The bulk protocols displayed in Sections 4.1.1, 4.2.1 and 4.3.1 are for consecutive bulk product whose starting dates cover the following periods of time.

Measles Virus - [redacted]

Mumps Virus - [redacted]

Rubella Virus - [redacted]

As seen in the respective product summaries for each virus, the consistency of assay results are typical for each product.

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Table 4.1 Batch Analysis - Measles Virus Bulk

Assay	Lot Number [redacted]
CONTROL CELLS	[redacted]
Hemadsorption	
CONTROL POOL (Test for adventitious agents)	
[redacted]	
Mycoplasma	
Avian Leukosis	
VIRUS HARVEST	
Sterility	
$TCID_{50}$-log_{10}/0.1 mL	
PRECLARIFIED	
(Test for adventitious agen	
[redacted]	
Sterility	
Mycoplasma	
FINAL BULK	
Identity	
Intact cells	
Sterility	
Protein nitrogen mg/mL	
Potency	
$TCID_{50}$-log_{10}/0.1 mL	
DATE OF RELEASE	

[redacted]/8

Table 4.2a Batch Analysis - Mumps Virus Bulk

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A4

Batch Analysis
Summary of Results
Mumps Virus
Lot Number [redacted] – Composed of Bulk Lots

Assay	[redacted]
CONTROL CELLS	
Hemadsorption	
CONTROL POOL	
(Test for adventitious age	
[redacted]	
Mycoplasma	
Avian Leukosis	
VIRUS HARVEST	
Sterility	
$TCID_{50}$-log_{10}/0.1 ml	
PRECLARIFIED	
(Test for adventitious age	
[redacted]	
Sterility	
Mycoplasma	
FINAL BULK	
Identity	
Intact cells	
Sterility	
Protein nitrogen mg/mL	
Potency	
$TCID_{50}$-log_{10}/0.1 mL	
DATE OF RELEASE	

Table 4.2b Batch Analysis - Mumps Virus Bulk

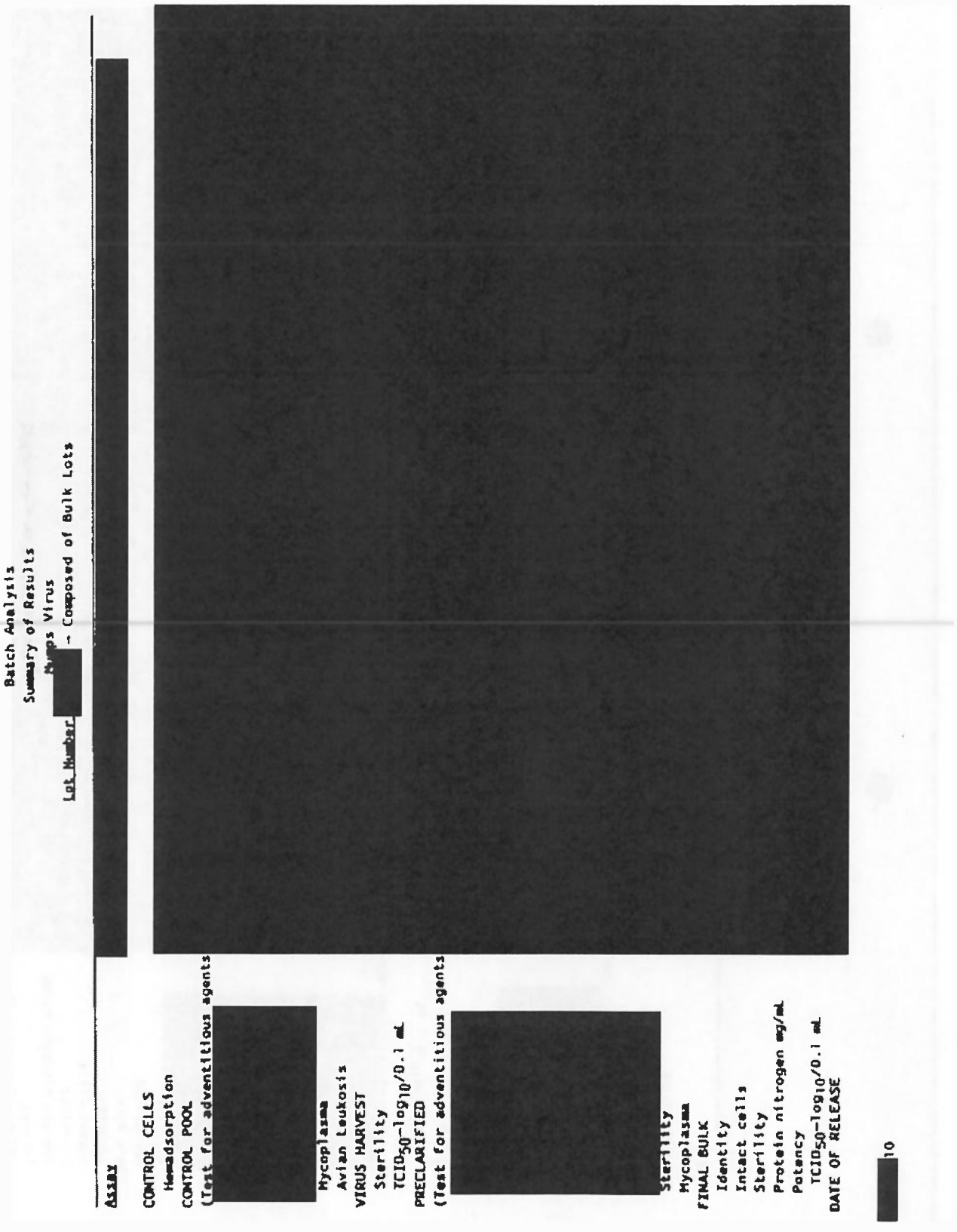


Table 4.2c Batch Analysis - Mumps Virus Bulk

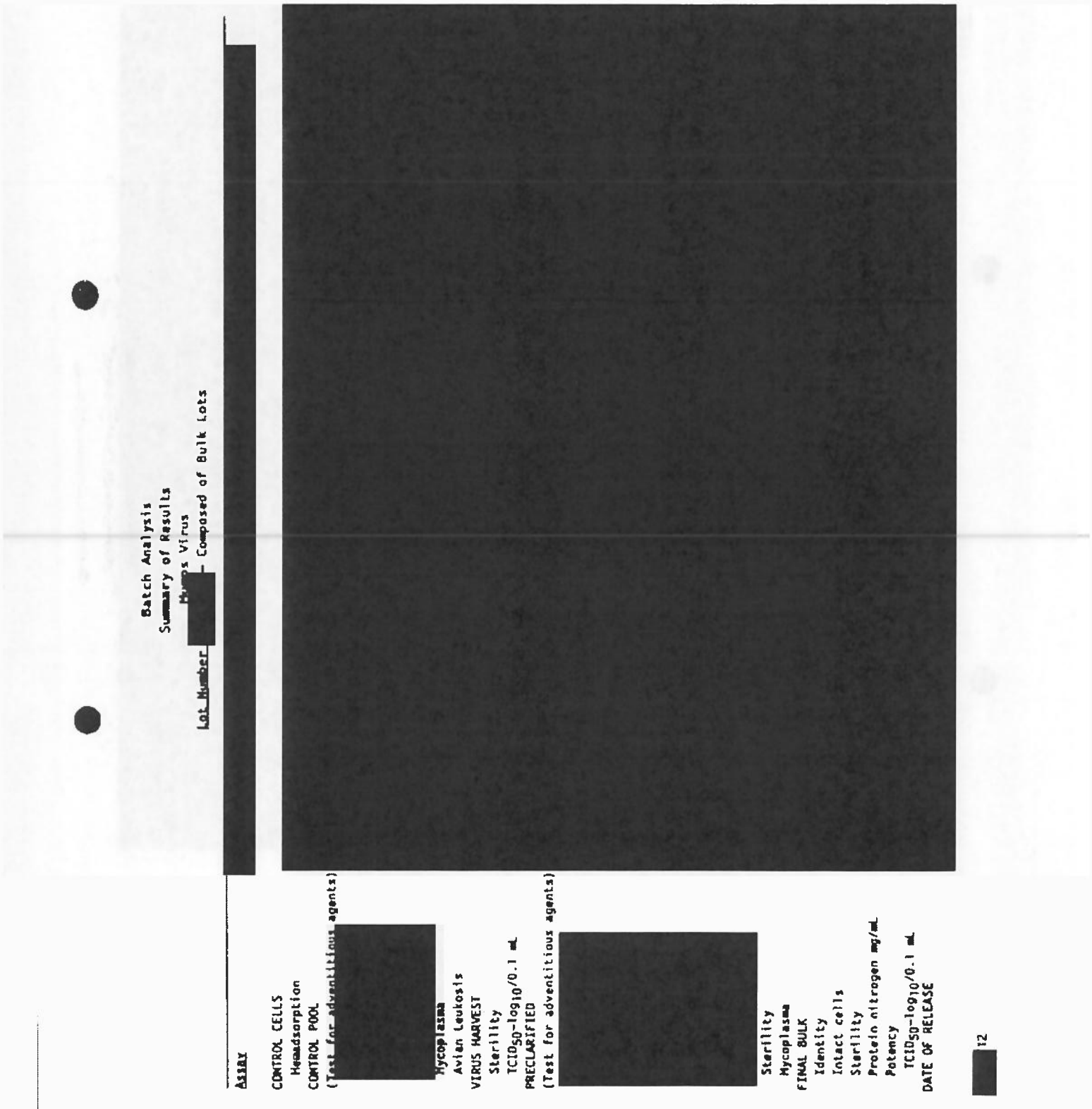
Batch Analysis
Summary of Results
Mumps Virus
Lot Number [redacted] - Composed of Bulk Lots

Assay	[redacted]
CONTROL CELLS	
Hemadsorption	
CONTROL POOL	
(Test for adventitious agen	
[redacted]	
Mycoplasma	
Avian Leukosis	
VIRUS HARVEST	
Sterility	
$TCID_{50}$-log_{10}/0.1 mL	
PRECLARIFIED	
(Test for adventitious agen	
[redacted]	
Sterility	
Mycoplasma	
FINAL BULK	
Identity	
Intact cells	
Sterility	
Protein nitrogen mg/mL	
Potency	
$TCID_{50}$-log_{10}/0.1 mL	
DATE OF RELEASE	

[redacted]/11

A2
A3
A4

Table 4.2d Batch Analysis - Mumps Virus Bulk



A2
A3
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Table 4.2e Batch Analysis - Mumps Virus Bulk

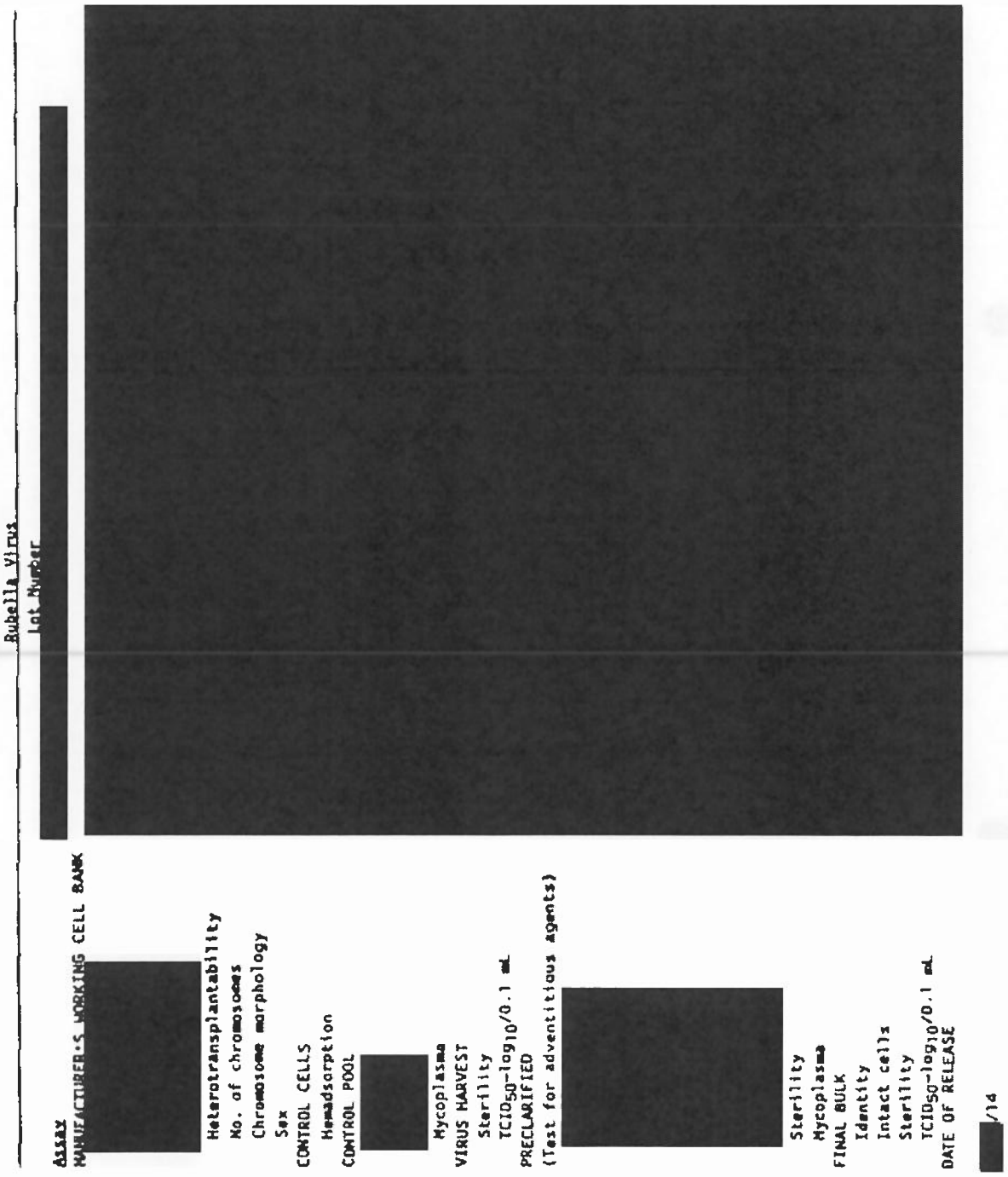
Batch Analysis
Summary of Results
Mumps Virus
Lot Number [redacted] - Composed of Bulk Lots

Assay	[redacted]
CONTROL CELLS	
Hemadsorption	
CONTROL POOL	
(Test for adventitious agents	
[redacted]	
Mycoplasma	
Avian Leukosis	
VIRUS HARVEST	
Sterility	
$TCID_{50}$-log_{10}/0.1 mL	
PRECLARIFIED	
(Test for adventitious agents	
[redacted]	
Sterility	
Mycoplasma	
FINAL BULK	
Identity	
Intact cells	
Sterility	
Protein nitrogen mg/mL	
Potency	
$TCID_{50}$-log_{10}/0.1 mL	
DATE OF RELEASE	

[redacted]/13

A2
A3
A4

Table 4.3 Batch Analysis - Rubella Virus Bulk



PART IID: CONTROL OF INTERMEDIATE PRODUCTS

There are no intermediate products

PART IIE CONTROL TESTS ON THE FINISHED PRODUCTS

Specifications

M-M-R®II is tested against the following specifications, which meet the compendial references described in Table 1.1.1, Compendial References for Live Virus Vaccines.

Identity

Each strain is neutralized by homologous antiserum.

Moisture

A maximum of 3.0%.

Sterility

Meets compendial requirements.

Safety

Meets EP requirement for Abnormal Toxicity.

Potency - per dose

Measles	1,000 $TCID_{50}$
Mumps	20,000 $TCID_{50}$
Rubella	1,000 $TCID_{50}$

Table 1.1.1 Compendial References for Live Virus Vaccines

TEST	European Pharmacopoeia	21 CFR	WHO (RBS)	USP	
IDENTITY	Monograph 213 Monograph 536 Monograph 182	630.36(a) 630.56(a)	No. 12, Part A,5.1 No. 38, Part A,5.1 No. 24, Part A,5.1		
MOISTURE		610.13(a)	No. 38, Part A,5.6 No. 24, Part A,5.5		
STERILITY	V.2.1.1	610.12	No. 12, Part A,5.2 No. 38, Part A,5.5 No. 24, Part A,5.2	<71>	
SAFETY	V.2.1.5	610.11	No. 12, Part A,5.4 No. 38, Part A,5.3 No. 24, Part A,5.4	<87>	
POTENCY	Monograph 213 Monograph 536 Monograph 182	630.34 630.54 630.64	No. 12, Part A,5.3 No. 38, Part A,5.2 No. 24, Part A,5.3	Monograph for Measles, Mumps and Rubella Virus Vaccine Live	
	213-Measles 536-Mumps 182-Rubella		No. 12-Measles No. 38-Mumps No. 24-Rubella	< >- USP General Tests and Assays	

continued

Test Methods Page IIE-3

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Identity

i) Test Method

Vaccine samples are constituted with diluent and mixed with appropriate homologous and heterologous antisera as seen in the following table. Aliquots are inoculated into sensitive cell culture systems after an appropriate holding period.

Virus component	Heterologous system	Homologous plus heterologous system	Sensitive culture system
measles	mumps & rubella	measles, mumps & rubella	[redacted]
mumps	mesles & rubella	measles, mumps & rubella	
rubella	mumps	mumps & rubella	

* Measles virus does not produce any cytopathic effect in [redacted] cells and [redacted].

ii) Test Evaluation

Cultures are examined microscopically at the completion of a [redacted] incubation period. A satisfactory identity test will exhibit specific neutralization of homologous virus demonstrated by at least a [redacted] reduction of virus expression in cultures containing homologous antiserum and the absence of neutralization of virus cytopathology in cultures containing heterologous antiserum.

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Moisture

i) Test Method

The [redacted] moisture analyzer is a fully automated apparatus which employs the Karl Fischer method for determining moisture content. The apparatus examines carefully weighed samples, corrects for interfering reactions, and displays the total moisture content in terms of percent of sample weight.

ii) Test Evaluation

Residual moisture must not exceed 3.0% by the [redacted] analysis. Upon the basis of data showing comparative results between the P_2O_5 compendial assay and the [redacted] the United States FDA approved use of this alternative test procedure, which has been used successfully since 1980.

Sterility

i) Test Method

The contents of [redacted] single-dose containers or [redacted] from each of [redacted] multiple-dose containers, reconstituted with appropriate diluent, are pooled and filtered through a [redacted] membrane. The membrane is rinsed with [redacted] volumes of [redacted] and aseptically cut into two parts. One-half of [redacted] is placed into [redacted] of fluid thioglycolate medium and one-half is placed into soybean-casein digest medium. The test containers are incubated at 30-35°C and 20-25°C, respectively.

ii) Test Evaluation

The test containers are examined visually at [redacted] for evidence of microbial growth. The test is satisfactory if no microbial growth is observed.

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Safety

i) Test Method

Filled containers of the final vaccine are each restored as directed with diluent and pooled. [redacted] guinea pigs weighing less than [redacted] are each injected intraperitoneally with [redacted]. [redacted] (or [redacted] mice, European Pharmacopoeia) weighing less than [redacted] are each injected intraperitoneally with [redacted]

ii) Test Evaluation

The animals are observed for 7 days. If, at the end of the test period, the animals survive and they weigh no less than at the time of injection and do not exhibit any response which is not specific or expected from the product, the test is satisfactory.

Potency Test

i) Test Method

Vaccine samples are constituted with diluent and mixed with appropriate heterologous antiserum as described under Section 1.1.2.1, Identity Testing. Serial dilutions are made of aliquots and inoculated into sensitive cell culture systems. Aliquots of calibrated reference virus preparations are tested also as control of assay technique and cell sensitivity. The potency of the calibrated reference virus preparation must fall between predetermined statistical limits in order for the sample test results to be considered valid.

ii) Test Evaluation

The measles component must contain no less than 1,000 $TCID_{50}$ per dose as determined in sensitive [redacted] cell culture. The mumps component must contain no less than 20,000 $TCID_{50}$ per dose as determined in sensitive [redacted] Cell culture. This value is equivalent in potency to 5,000 $TCID_{50}$ per dose as determined by titration in [redacted] cell cultures of less sensitivity to mumps virus. The rubella component must contain no less than 1,000 $TCID_{50}$ per dose as determined in sensitive [redacted] cell culture.

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iii) Reference Standards

The house standards for measles, mumps and rubella vaccines consist of final containers of released lots of the monovalent vaccines which are stored at [redacted] or below. The potency of the house standards has been established by repeat testing in the release potency assay ($TCID_{50}$).

The house standards are tested on each test day and used to monitor and control the performance of the potency assays. Action limits of [redacted] standard deviations around the established mean potency of the house standard are used to invalidate entire test runs for which the house standard does not fall within the established range.

Sample potency results are not corrected or adjusted based on the house standard results.

Measles Virus

The current measles vaccine house standard (measles house standard [redacted]) is ATTENUVAX® Lot [redacted] which was released by CBER on [redacted]. The currently established potency limits for measles house standard [redacted] are [redacted] Test runs in which the potency of measles house standard [redacted] falls outside of this range are considered invalid and are repeated.

Vials of measles house standard [redacted] were submitted to CBER for use as a reference vaccine. This house standard has been in use in the Merck laboratory since [redacted]

Mumps Virus

The current mumps vaccine house standard (mumps house standard [redacted]) is MUMPSVAX® Lot [redacted] which was released by CBER on [redacted]. The currently established potency limits for mumps house standard [redacted] are [redacted] Test runs in which the potency of mumps house standard [redacted] falls outside of this range are considered invalid and are repeated.

Vials of mumps house standard [redacted] were submitted to CBER for use as a reference vaccine.

This house standard has been in use in the Merck laboratory since [redacted].

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Rubella Virus

This current rubella vaccine house standard (rubella house standard [redacted] is MERUVAX®II Lot [redacted] which was released by CBER on [redacted]. The currently established potency limits for rubella house standard [redacted] are [redacted] Test runs in which the potency of rubella house standard [redacted] falls outside this range are considered invalid and are repeated. This house standard has been in use in our laboratory since [redacted]

The previous rubella house standard, MERUVAX®II Lot [redacted] had final potency limits of [redacted] and was in use in the Merck laboratories from [redacted] through [redacted] Vials of rubella house standard [redacted] were submitted to CBER for use as a reference standard.

SCIENTIFIC DATA **Page IIE-8**

Validation of analytical methods **Page IIE-8**

Moisture Test

The following methodology was reviewed and approved by the U.S. Food and Drug Administration for use as an alternate procedure for determination of moisture content in Merck and Co., Inc. live virus vaccines.

Studies were performed on comparative moisture testing data between the [redacted] test and the [redacted], which is an automatic apparatus for Karl Fischer moisture titration. The experiment was performed on two composite test samples ([redacted] vials each) by the [redacted] method and [redacted] vials individually tested by [redacted] on each filling of [redacted] live virus vaccines - monovalent and combinations.

The results of the analyses showed the following:

1. The resulting linear fit of the regression analysis after elimination of extreme results indicates a consistent difference over the range of values between the two methods.

2. No significant difference was detected among the [redacted] vaccines.

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3. The [redacted] results demonstrate a [redacted] average moisture content than results obtained using the [redacted] method. Over the range of moisture studied this value amounted to a level of [redacted] per sample. Therefore, using the [redacted] method of assay a comparative release limit of no greater than 3.0% moisture was approved by the US Food and Drug Administration, Center for Biologics Evaluation and Research (then the Center for Biologics) on January 16, 1980.

4. A confidence level of [redacted] calls for [redacted] vials from each filled lot to be tested.

Incorporation into routine use has showed the assay results to be accurate and reliable and has reduced testing time per sample from [redacted] to [redacted].

The U.S. Food and Drug Administration approved the methodology for use on January 19, 1980 with an adjusted release limit of $\leq 3.0\%$ as determined by [redacted] methodology.

Batch analysis of finished product **Page IIE-11**

Summary of Results

The results of testing of the finished product for [redacted] consecutive fillings during the period January 6, 1992 and January 17, 1992 are seen in Table 2.2.1. These results are typical for this formulation of vaccine which has been produced by Merck and Co., Inc. for nearly fourteen years. A12

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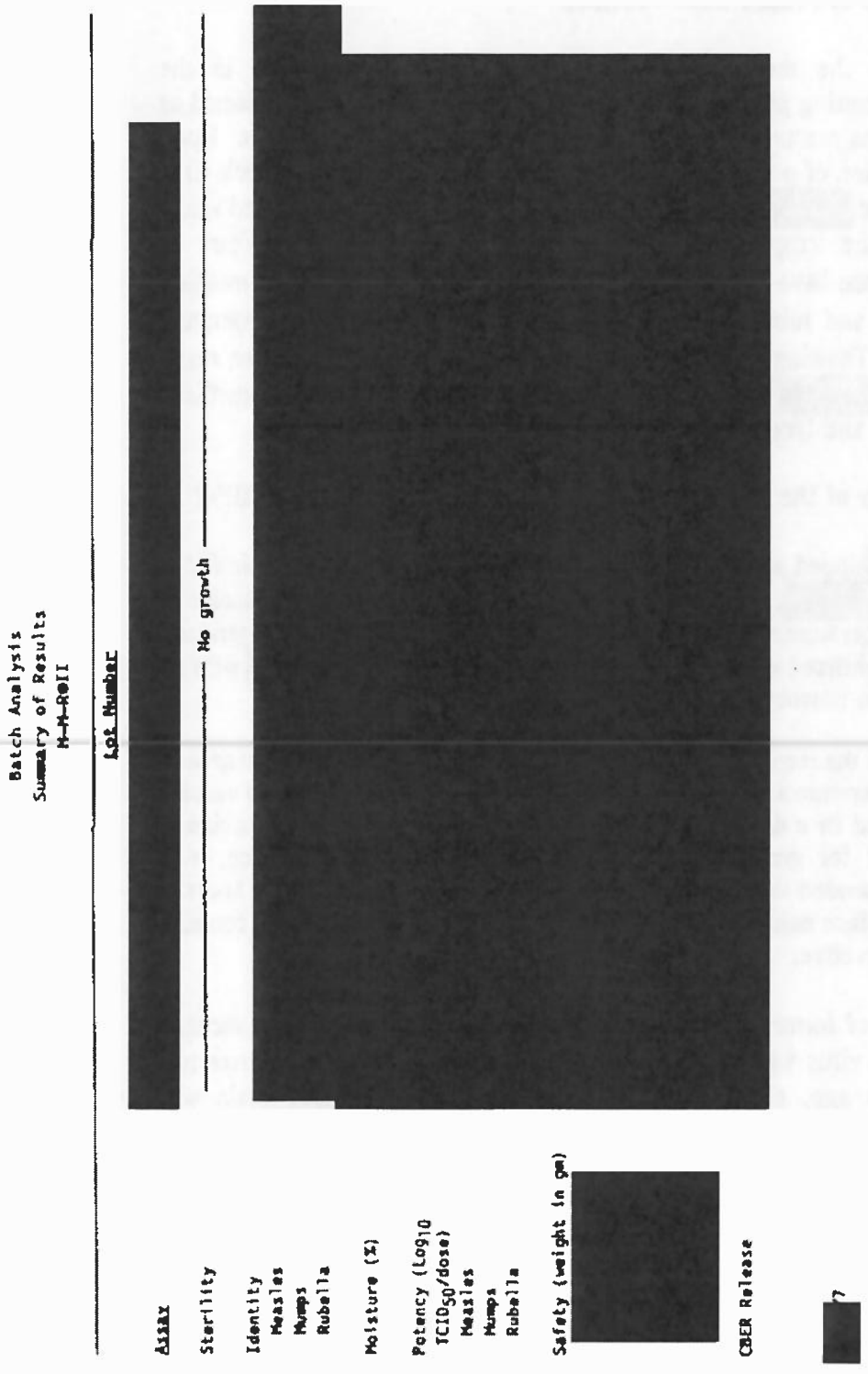
Table 2.2.1 Batch analysis of the finished product



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PART IIF: STABILITY DATA Page IIF-1

Stability of Frozen Bulk Vaccines

Due to the thermolabile nature of the vaccine, all steps in the manufacturing procedure for bulk and finalized product are conducted as rapidly as practical to insure integrity and stability of the product. Upon completion of pooling operations, aliquots of the bulk pool for each virus strain are [redacted] and immediately transferred to refrigerated vaults where the temperature is maintained at less than [redacted]. Years of experience have shown that the concentration of infectivity for measles, mumps and rubella virus is maintained by storage at this temperature range. Thawing of the bulk aliquots months and even years later, result in [redacted] upon completion of standardized dilution and lyophilization.

Stability of the Finished Product Page IIF-2

When shipped at [redacted] the lyophilized vaccine is stable for at leas[redacted]. Although most facilities store the lyophilized vaccine in the temperature range of [redacted] which is standard for normal refrigerators, the lyophilized vaccine may be stored at temperatures [redacted] with no effect on potency.

Virus in the reconstituted vaccine is subject to degradation by light as well as temperature and, therefore, it is recommended that reconstituted vaccine be stored in a dark place at 2-8°C. Although potency of the vaccine is retained for greater than 24 hours at 2-8°C after reconstitution, it is recommended that the reconstituted vaccine be discarded after 8 hours at 2-8°C, since neither the lyophilized vaccine nor the sterile diluent contains a preservative.

In lieu of formal extended stability studies when measles virus vaccine, mumps virus vaccine and rubella virus vaccine were licensed over two decades ago, surplus infectious attenuated virus of each strain was incorporated into the initial formulation of vaccine at the time of introduction. A release limit of no less than 1,000 $TCID_{50}$ was established for measles virus and rubella virus and a release limit of no less than 5,000 $TCID_{50}$ for mumps virus.* Expiry of each was established at [redacted], which was changed later to [redacted] upon the basis of data developed from long-term stability studies.

* Mumps virus at that time was tested for potency using [redacted] cells.

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Stability at 2-8°C **Page IIF-4**

The formal stability study program policy calls for [redacted] of each formulation to be selected annually, if available, at random and samples from the selected lot to be entered into the test program for a period extending for [redacted] beyond expiry of the selected lot.

The data in Tables 2.1.a through 2.1.d show retention of viral infectivity for each strain throughout the period of study. Potency is measured by standard microtiter assay procedures and the results expressed as Tissue Culture Infectious Dose$_{50}$ ($TCID_{50}$), i.e., [redacted] based upon the volume of inoculum per culture well in the test series. Minimum requirements for each strain under this method are as follows:

[redacted]

Measles virus
Mumps virus
Rubella virus

[redacted]

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Table 2.1.a M-M-R®II Stability at 2-8°C

M-M-R®II

Stability at 2-8°C

Lot	Interval (months)	Measles	Mumps	Rubella
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	15			

Table 2.1.b ATTENUVAX® Stability at 2-8°C

ATTENUVAX®

Stability at 2-8°C

Interval (months)	Potency [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]16

Table 2.1.c MUMPSVAX® Stability at 2-8°C

MUMPSVAX®

Stability at 2-8°C

Interval (months)	Potency [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]17

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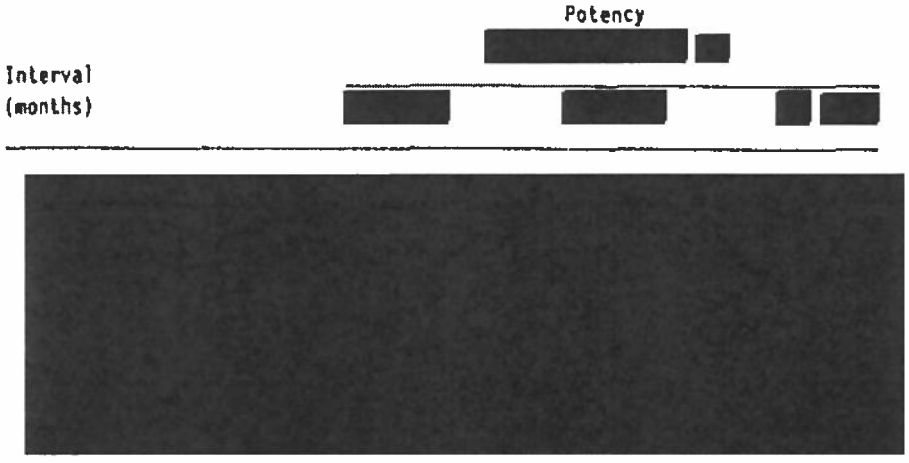
Table 2.1.d MERUVAX®II Stability at 2-8°C

MERUVAX®II

Stability at 2-8°C



[redacted]18

Expanded Stability Studies

Summary of Long-Term Stability Data

In order to evaluate the long-term stability of each strain, data from both formal stability studies and data from studies where normal CBER released lots have been used as controls for long-term studies of experimental vaccines, are progressively collated and analyzed.

Summaries of such data for all formulations utilizing measles virus, mumps virus and rubella virus are given in Tables 2.2.1.a through 2.2.1.h on pages **Page IIF-10 to IIF-17 of Part II.** The data are expressed as the $\log_{10}$ of potency loss per year as determined by linear regression analyses.

These data demonstrate for each strain and each formulation that throughout the period of expiry that each formulation of vaccine retains potency in excess of the minimum effective dose of each strain, when stored as prescribed by license and as expressed in the package circular developed for each formulation.

Stability of Vaccine at Elevated Temperatures Page IIF-18

When subjected to temperatures above the required storage temperature range, the lyophilized vaccines in both monovalent and multivalent form degrade more rapidly than vaccine which has been properly stored.

Although a reduction of approximately [redacted] as seen after [redacted] at [redacted] for both measles virus and mumps virus still results in vaccine potency in excess of the minimum effective dose, the data nevertheless demonstrate the adverse effects of elevated temperature and emphasize the need for proper shipping and storage procedures.

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Stability of Reconstituted Vaccine

A summary of the data from studies of the stability of reconstituted vaccine is seen in Table 2.2.3. In these studies samples of monovalent and multivalent vaccine were restored with the proper volume of diluent as prescribed for inoculation of vaccinees and stored at 2-8°C, which is the recommended storage temperature range for all Merck live virus vaccines. At intervals of [redacted] after restoration, samples were

inoculated into susceptible cell culture systems used for determination of potency and the amount of residual infectious virus was determined. Linear regression analyses were performed on the mean potency values found at each time interval with the resultant slopes averaged to determine potency loss.

Table 2.2.3. Stability of Reconstituted Measles Virus, Mumps Virus and Rubella Virus at 2-8°C for 24 hours

	Average Loss (log_{10})	Standard Deviation
Measles Mumps Rubella	[redacted]	

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Although [redacted] of infectious virus of each strain [redacted] in suspension after 24 hours at 2-8°C, discard of the reconstituted vaccine is recommended because of the absence of a preservative.

PART IIQ: OTHER INFORMATION

Complete and detailed information is provided on the details of the manufacturing facilities for manufacture of M-M-R®II, including buildings and facilities, floor plans, animal facilities, equipment, labelling of products, retention of samples, organization of responsible personnel; such as are included in the United States Establishment License for the product (Establishment License #002).

INFORMATION ON THE AUTHOR

[redacted]

C

[redacted]

Extension Directives 89/342 and 89/381 EEC

C

M-M-R®II

Measles, Mumps and Rubella Vaccine, Live, MSD

Expert Report on the

Toxicological and Pharmacological Documentation

By:.... [redacted] .....

Merck Research Laboratories
West Point, Pennsylvania, 19486, USA

November 20, 1992

The documentation in this volume also supports the monovalent vaccines;

ATTENUVAX® (Measles Vaccine, Live, MSD)
MUMPSVAX® (Mumps Vaccine, Live, MSD)
MERUVAX®II (Rubella Vaccine, Live, MSD)

and bivalent combinations of these vaccines;

BIAVAX®II (Rubella and Mumps Vaccine, Live, MSD)
M-M-VAX® (Measles and Mumps Vaccine, Live, MSD)
M-R-VAX®II (Measles and Rubella Vaccine, Live, MSD)

1. PRODUCT PROFILE

a) Type of application

The application is for the relicensing, under the implementation of Extension Directives 89/342 EEC and 89/381 EEC, of a product which is already licensed and on the market in the member state where this application is made.

b) Chemical and pharmacokinetic properties

The vaccine is a triple antigen containing (1) **ATTENUVAX®** (Measles Virus Vaccine, Live), a more attenuated line of measles virus derived from Enders' attenuated Edmonston strain and grown in cell cultures of chick embryo; (2) **MUMPSVAX®** (Mumps Virus Vaccine, Live), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) **MERUVAX®II** (Rubella Virus Vaccine, Live), the Wistar RA27/3 strain of live attenuated rubella virus grown in human diploid cell (WI 38) culture. Pharmacokinetic studies have not been conducted on the live virus vaccine, which is administered subcutaneously.

c) Indications

For simultaneous immunization against measles, mumps and rubella in persons 15 months of age and older.

d) Precautions

Adequate treatment provisions, including adrenalin, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur. Due caution should be employed in administration of M-M-R®II in persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevations which may occur following vaccination.

Children and young adults who are known to be infected with human immunodeficiency viruses but without clinical manifestations of immunosuppression may be vaccinated; however the vaccinees should be monitored closely for vaccinee-preventable diseases because immunization may be less effective than for uninfected persons.

Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of human immune serum globulin.

Excretion of small amounts of the live attenuated rubella virus from the nose or throat has

occurred in the majority of susceptible individuals 7-28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.

There are no reports of transmission of the live measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R®II. Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine; no studies have been reported to date of the effect of live measles virus vaccines on untreated tuberculous children. As for any vaccine, vaccination with M-M-R®II may not result in seroconversion in 100% of susceptible persons given the vaccine.

Pregnancy

Animal reproduction studies have not been conducted with M-M-R®II. It is also not known whether M-M-R®II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination.

Nursing mothers

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating post-partum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Caution should be exercised when M-M-R®II is administered to a nursing woman.

e) **Marketing/post-marketing**

M-M-R®II was first licensed in the United States of America on September 15, 1978, and is now licensed in more than 30 countries, worldwide. During the period 1978 to 1992, over [redacted] doses of this vaccine have been supplied worldwide. A16

2. EXPERT REPORT

2.1 Introduction Page IIIA-1

M-M-R® II is a trivalent combination of live, attenuated measles, mumps and rubella viruses. It is indicated for routine immunization against disease caused by measles virus, mumps virus and rubella virus in infants and children 15 months of age or older.

The individual virus strains which comprise this vaccine were developed separately, as described in Part II of the Marketing Authorization Application (MAA), and thus have their own unique histories. As "live", attenuated viruses, however, they share a single mechanism for their development.

A virulent virus is isolated from a patient and is subsequently propagated in tissue culture cells. These cells are either of non-human origin or derived from human tissue different from the type in which the virus normally causes disease, or both. At various stages of propagation, or passage levels, the virus is tested for attenuation in susceptible human volunteers. An appropriately attenuated virus is one

which does not cause clinical disease but does induce protective immunity. Clearly, the development of live, attenuated viral vaccines is an empirical process.

A classic example of attenuated vaccine development is described by Stokes et al. (Pediatrics 39:363-371, 1967)[1]. The Jeryl Lynn mumps strain was administered to children at two different levels of passage in chick embryo cells. Both were immunogenic, but the lower passage level virus caused a low incidence of parotitis while the higher passage level virus did not. The higher passage virus was developed for commercial use and is the virus included in M-M-R® II.

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1 see References, page 7

2.2 Toxicity Pages IIID-6; IIIE-15; IIIF-17

Sub-acute and long-term toxicity studies usually applied to drugs to be administered chronically would be inappropriate for a live attenuated viral vaccine. This vaccine is intended for administration once in infancy and, in the United States, a second time as a booster on school entry. However, the components of M-M-R® II are submitted to an extensive testing regimen, outlined in Parts II and III of the MAA which assures safety, sterility and freedom for adventitious agents.

2.3 Pharmacodynamics Page IIIG-19 and Part IV

While live, attenuated viruses are not alive in the strict sense of the word, they are infectious. Immunity is induced by a subclinical infection characterized by limited viral replication and activation of both the CD4-MHC class II and the CD8-MHC class I arms of the immune system. Since attenuated viruses do replicate in the vaccinee, immunity may be raised against a spectrum of viral proteins, both structural components of the virion and non-structural proteins involved in the replication process. The result is a broadly-based response ranging from antibodies against a variety of epitopes on the virion to

cytotoxic T-lymphocytes specific for infected cells. This breadth of response allows a vaccinee to make an overall protective response even if he should, by virtue of having a particular MHC haplotype, be incapable of responding to a single particular viral antigen. Live, attenuated viral vaccines also generally induce long-testing immunity after a single dose.

2.4 Immunogenicity **See Part IV**

Viral infectivity, pathogenicity and attenuation are generally host species specific. Therefore, credible animal models of viral infectious diseases continue to be an important missing element in vaccine development.

This was especially true during the 1960's when the individual virus strains comprising M-M-R® II were developed. Vaccines were developed empirically, following clinical symptoms, virus excretion, appearance of neutralizing antibodies, and appearance of hemagglutination inhibiting antibodies as correlates of protection and attenuation. It has been difficult to single out unique targets of protective immunity for any of these viruses.

2.5 Pharmacokinetics

See Part IV

The usual range of experimental studies applied to drugs to demonstrate absorption, distribution, metabolism and excretion of an active ingredient are inappropriate for evaluation of live, attenuated viral vaccines. It is known that subcutaneous injection of a vaccine results in a limited subclinical infection. Excepting for rubella, detectable virus is not excreted, indeed this is one of the benchmarks of attenuation. Infectivity of the vaccine is important, since inactivated vaccines (heated or fixed) elicit only a transient immune response after a single dose.

Overall Conclusions **Page IIIG-19 and Part IV**

M-M-R® II is highly immunogenic in children. Universal vaccination with M-M-R® II in the United States has virtually eliminated measles, mumps and rubella as common diseases of childhood. The few outbreaks which have occurred are largely attributable to failure to vaccinate. Recent antibody persistence studies with measles and mumps virus vaccines show that over 90% of vaccinees retain a neutralizing titer for 13 years. Long-term data on antibody persistence for rubella virus vaccine are to be forthcoming.

M-M-R® II in its present formulation has been registered in the United States since 1978 and over [redacted] doses have been administered worldwide. The vaccine is generally safe and well-tolerated as indicated by the pharmacovigilence section in Part IV of the MAA. Thus, the vaccine is efficacious and safe for use in humans.

A16

I have been involved in the development of attenuated viral vaccines for over two years and in virology for ten years.

[redacted]

C

References.

1. Stokes, et al. *Pediatrics* 39: 363-371, 1967

Reprinted from *Pediatrics*, Vol. 39, No. 3
March, 1967

LIVE ATTENUATED MUMPS VIRUS VACCINE. II. EARLY CLINICAL STUDIES

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MUMPS is a common childhood disease that may be severely and even permanently crippling when it involves the brain, testis, ovary, auditory nerves or pancreas. Adult males may be permanently sterilized by mumps. Time loss from productive effort, the occasional serious clinical consequence of natural mumps virus infection, and the personal discomfort from the illness justify application of a safe and effective live virus vaccine. A previous report[1] in the present series described the development of a live attenuated mumps virus vaccine designated Jeryl Lynn strain level B. The present report describes the clinical, virologic and serologic findings obtained in children in institutions who were vaccinated with level B Jeryl Lynn strain vaccine or with less attenuated level A of the same virus. Other reports[2-4] describe the clinical findings, serologic responses, and protective efficacy of B level Jeryl Lynn strain vaccine in a large controlled field study carried out in children during 1965 and 1966.

MATERIALS AND METHODS

Vaccine

The B level and A level Jeryl Lynn strain viruses were grown in cell cultures of chick embryo derived from a leukosis-free chicken flock. Lots 137 (B level, seventeenth passage) and 138 (A level, twelfth passage) vaccines were tested for safety and potency by methods consistent with the standards for live measles virus vaccine specified in the Standards of the U.S. Public Health Service[5] for live measles virus vaccine. The product was dried and was rehydrated just prior to use in children. Details relating to the development and preparation of the vaccine were presented in an earlier report.[1] The infectivity titer of level A lot 138 vaccine was $10^{4.9}$/0.1 ml and of level B lot 137 was $10^{3.6}$/0.1 ml as measured in grivet monkey kidney cell cultures (GMK) and using the hemadsorption endpoint.

Conduct of the Studies

Studies 1 and 2 were carried out in children in the Trendler Nursery School and the Merna Owens Home. These institutions are for the mentally retarded and are located in Pennsylvania. The investigations were done with the concurrence of the medical and supervisory staffs of the institutions and with the approval of the Pennsylvania Association for Retarded Children.* Following initial bleeding, a throat specimen was collected by swab which was also firmly applied to Stensen's duct and extracted into sterile veal infusion broth. The children were given 0.5 ml or 1.0 ml of rehydrated vaccine subcutaneously. Throat specimens were collected in the same manner as above on days 8, 10, 14, 17, and 21 following vaccine to test for mumps virus excretion. Blood samples were taken at the time intervals shown in the text. The broth specimens were stored frozen at —65°C

* In obtaining approval for such studies, a primary consideration has been the fact that the vaccinations could do no harm but might be of benefit to the subject himself and to his family.

• Received July 29; revision accepted for publication October 14, 1966.)

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in a mechanical deepfreeze until tested. The serum samples were stored frozen at −20°C in a mechanical unit. Oral temperatures were taken twice daily for 28 days and the patients were under continuous surveillance by the nursing staff and the physicians. All temperatures and other clinical findings were recorded.

The children in study 3 were inoculated, with parental consent, in the pediatric outpatient clinic at Lankenau Hospital, Overbrook, Pennsylvania, a suburb of Philadelphia. Serial dilutions of the vaccine were prepared in medium 199 with viral stabilizer for purpose of titrating the least dose of virus required to immunize. The volume was 1.0 ml given subcutaneously. Blood samples were drawn initially and on the twenty-eighth day following vaccine. A report card for each child was given to the parent for recording temperatures once daily plus any other illness which occurred and the parents were asked to notify one of us (R.E.W.) immediately when any illness occurred. Any patient with a reported significant illness was seen by one of us (R.E.W. or J.S., Jr.). The children were observed by the parent for 28 days and the report cards were returned at the time of the visit for the second blood sample.

Laboratory Tests

Serum neutralization and hemagglutination-inhibition (HI) titrations of the patients' sera were carried out as described previously.[1] Serum amylase determinations were performed by Dr. Howard Rawnsley of the Pepper Laboratory of Clinical Medicine, University of Pennsylvania, according to the method of Peralta and Reinhold.[6] Virus isolation attempts were made in cell cultures of grivet monkey kidney (GMK). For this purpose, the thawed throat specimens were diluted 1:2 with a medium containing an antibiotic mixture and were planted in 0.5 ml amount in quadruplicate in GMK tubes. The cultures were rotated in a drum at 36°C and were observed for cytopathic effect on the third, fifth, and seventh days of incubation. One subculture passage was made in the same manner on day 7 and the cell sheets were examined for mumps cytopathology and for presence of a hemadsorbing virus, using guinea pig erythrocytes, at the termination of each passage. All isolated viruses were identified in appropriate tests with known positive antisera prepared in animals.

RESULTS

Study 1

Groups of children in the Trendler Nursery School who were initially without mumps antibody were inoculated subcutaneously with 1.0 ml amount of passage level B (lot 137) or level A (lot 136) Jeryl Lynn strain live attenuated mumps virus vaccine or were held as uninoculated contact controls. Vaccination was carried out on June 28, 1965. The findings are presented in Tables I, II, and III. Serum specimens for antibody titration and for amylase values and throat specimens for virus isolation were collected at the time periods shown in Table I. The children in the study ranged in age from 1 to 10 years (average, 5 years) and were in contact with each other.

All children responded serologically with the development of both neutralizing and HI antibody within 28 days following vaccine. Neutralizing antibody was present in most children within 14 days following vaccine but HI antibody usually appeared later in the infection. Neutralizing antibody following lot 137 (level B) vaccine persisted for at least 7 months with fourfold or greater diminution of titer noted in only 4 of the 12 children from whom specimens were available. The reduction in mean titer from 1:11 initial to 1:4 was due in part to loss from the study of two children whose 28-day blood samples were of high titer, i.e., 1:16 and 1:32. None of the uninoculated contact controls developed mumps antibody, even after 3 to 7 months following vaccine. This indicated failure of cross-infection from the vaccinated persons to the unvaccinated control children. The serum amylase values were not significantly altered in the vaccinated persons, which indi-

TABLE I

STUDY I. COMPARISON OF CLINICAL, VIROLOGICAL, AND SEROLOGICAL FINDINGS AMONG CHILDREN WHO WERE INITIALLY SERONEGATIVE FOR MUMPS AND WHO WERE GIVEN LEVEL B (LOT 137) OR LEVEL A (LOT 138) JERYL LYNN STRAIN LIVE MUMPS VIRUS VACCINE OR HELD AS CONTACT CONTROLS

Case Number	Mumps Virus Excretion from Throat on Day						Parotid Swelling (Day of Onset)*	Serologic Findings for Mumps at Time Period after Vaccine									Serum Amylase Values		
								Neutralization Titer						HI Titer					
	0	8	10	14	17	21		0 da	14 da	28 da	3 mo	5 mo	7 mo	0 da	14 da	28 da	0 da	14 da	28 da
Lot 137 Vaccine (Level B)																			
140	0	0	0	0	0	0	None	<1	N.D.	16	16	N.D.	N.D.	<8	<8	40	16	12	14
102	0	0	0	0	0	0	None	<1	N.D.	16	16	8	16	<8	<8	40	N.D.	94	12
135	0	0	0	0	0	0	None	<1	N.D.	16	16	16	8	<8	80	80	14	16	16
107	0	0	0	0	0	0	None	<1	N.D.	16	4	8	N.D.	<8	<8	16	16	12	14
106	0	0	0	0	0	0	None	<1	N.D.	16	32	32	16	<8	<8	16	8	94	16
115	0	0	0	0	0	0	None	<1	N.D.	16	4	8	8	<8	8	16	8	84	8
109	0	0	0	0	0	0	None	<1	N.D.	16	16	8	8	<8	16	80	80	80	12
116	0	0	0	0	0	0	None	<1	N.D.	16	4	8	8	<8	<8	16	8	16	8
100	0	0	0	0	0	0	None	<1	N.D.	8	8	8	8	<8	<8	16	8	8	32
132	0	0	0	0	0	0	None	<1	N.D.	8	8	8	4	<8	<8	16	16	8	16
104	0	0	0	0	0	0	None	<1	N.D.	8	4	8	8	<8	<8	16	16	40	16
120	0	0	0	0	0	0	None	<1	N.D.	8	4	4	4	<8	<8	8	4	8	16
102	0	0	0	0	0	0	None	<1	N.D.	4	8	4	4	<8	<8	16	4	16	8
118	0	0	0	0	0	0	None	<1	N.D.	4	4	4	8	<8	<8	8	16	64	16
							Mean†	<1		11	8	8	6	<8	8	18	10	17	14
Lot 138 Vaccine (Level A)																			
141	0	0	0	+	0	0	Yes (14)	<1	8	128	N.D.	N.D.	N.D.	<8	8	40	32	80	0
130	0	0	0	+	0	0	Yes (14)	<1	8	16	N.D.	N.D.	N.D.	<8	<8	40	80	80	14
95	0	0	0	+	+	0	No	<1	4	8	N.D.	N.D.	N.D.	<8	<8	40	8	16	12
103	0	0	0	0	0	0	Yes (10)‡	<1	<8	4	N.D.	N.D.	N.D.	<8	<8	8	12	16	4
90	0	0	0	0	0	0	Yes (10)	<1	8	128	N.D.	N.D.	N.D.	<8	<8	160	8	16	16
112	0	0	0	0	0	0	No	<1	16	128	N.D.	N.D.	N.D.	<8	<8	80	32	16	8
134	0	0	0	0	0	0	No	<1	16	32	N.D.	N.D.	N.D.	<8	16	80	8	16	16
138	0	0	0	0	0	0	No	<1	4	32	N.D.	N.D.	N.D.	<8	8	40	80	80	64
96	0	0	0	0	0	0	No	<1	8	16	N.D.	N.D.	N.D.	<8	<8	80	8	8	4
117	0	0	0	0	0	0	No	<1	4	16	N.D.	N.D.	N.D.	<8	<8	16	16	16	16
126	0	0	0	0	0	0	No	<1	<8	16	N.D.	N.D.	N.D.	<8	<8	16	16	16	8
128	0	0	0	0	0	0	No	<1	<8	16	N.D.	N.D.	N.D.	<8	<8	16	8	16	16
144	0	0	0	0	0	0	No	<1	4	16	N.D.	N.D.	N.D.	<8	16	16	8	4	64
97	0	0	0	0	0	0	No	<1	8	8	N.D.	N.D.	N.D.	<8	<8	8	4	16	8
114	0	0	0	0	0	0	No	<1	8	8	N.D.	N.D.	N.D.	<8	<8	16	64	80	16
110	0	0	0	0	0	0	No	<1	8	4	N.D.	N.D.	N.D.	<8	<8	8	16	16	8
							Mean†	<1	5	10				<8	8	18	19	16	11
Unvaccinated Controls																			
11 persons	0	0	0	0	0	0	No	<1	<1	<1	N.D.	N.D.	N.D.	<8	<8	<8	See Table II		
7 of above							No	<1	<1	<1	<1	N.D.	N.D.	<8	<8	<8			
1 of above							No	<1	<1	<1	<1	<1	<1	<8	<8	<8			

N.D. = Not done.
* Day of onset is indicated by numbers in parentheses.
† Geometric mean neutralizing and HI antibody titers; arithmetic mean amylase values.
‡ Surgerive parotitis.

cated a lack of significant damage to cells of the parotid glands or pancreas.

Three of 16 children who received lot 138 level A Jeryl Lynn vaccine and which was in the twelfth chick embryo and chick embryo cell culture passage excreted mumps virus from their throats and four of these children developed clinically apparent or suggestive parotitis. This indicated that the A level virus was not sufficiently attenuated for purpose of routine vaccination. None of the children who received lot 137 level B

TABLE II

SERUM AMYLASE VALUES FOR 18 UNINOCULATED CONTROLS FROM TABLE I

Case Number	Serum Amylase Values		
	0 da	14 da	28 da
100	14	16	16
101	8	2	22
104	6	16	24
106	18	14	18
111	2	2	6
113	14	2	6
116	16	16	30
118	2	20	24
125	38	18	2
128	8	14	14
131	6	16	10
139	8	22	6
141	8	12	4
A.M.:*	12	13	14

* Arithmetic mean.

Jeryl Lynn vaccine which was in the seventeenth chick embryo-chick embryo cell culture passage excreted mumps virus orally and none developed clinically apparent parotitis. The greater apparent virulence of level A virus for man was consistent with the higher titers of antibody which were obtained compared with level B vaccine, viz., neutralization and HI antibody titers of 1:19 and 1:18, respectively, for level A compared with 1:11 and 1:12, respectively, for level B.

The oral temperatures noted in the children during four different time periods following vaccination are summarized in Table III. Inspection of the data indicate no significant difference in maximal temperature or in numbers of fever days among recipients of lot 137 level B vaccine compared with the uninoculated controls. There was, however, a higher rate of fever of 103°F (0) or greater during the 5- to

TABLE III

STUDY 1. ORAL TEMPERATURES AMONG CHILDREN GIVEN LEVEL B (LOT 137) OR LEVEL A (LOT 136) JERYL LYNN STRAIN LIVE MUMPS VIRUS VACCINE COMPARED WITH CONTROLS

Maximal Temperature Recorded for the Period (oral, °F)	Time Period After Vaccination	Maximum Temperature Recorded			Total Days of Fever (99° F or >) Recorded: Grouped According to Maximal Temperatures for the Period					
		Lot 136 (A) (16 persons)	Lot 137 (B) (14 persons)	Controls (13 persons)	Lot 136 (A) (16 persons)		Lot 137 (B) (14 persons)		Controls (13 persons)	
					Total da	Average	Total da	Average	Total da	Average
<99	Days 1–4	6	8	3	—	—	—	—	—	—
99–100.9	Days 1–4	9	5	10	5	0.6	6.5	1.3	9.5	1.0
101–102.9	Days 1–4	1	0	0	1	1.0	0	—	0	—
103–104.9	Days 1–4	0	1	0	0	—	3	3.0	0	—
<99	Days 5–12	6	5	4	—	—	—	—	—	—
99–100.9	Days 5–12	8	9	8	9	1.1	8	0.9	17.5	2.0
101–102.9	Days 5–12	0	2	1	0	—	8.5	4.2	3	3.0
103–104.9	Days 5–12	2	0	0	6.5	3.2	0	—	0	—
<99	Days 13–18	9	8	7	—	—	—	—	—	—
99–100.9	Days 13–18	4	5	4	5.5	1.4	6.5	1.3	7	1.8
101–102.9	Days 13–18	2	1	2	9	4.5	6	6.0	6	3.0
103–104.9	Days 13–18	1	0	0	4	4	0	—	0	—
<99	Days 19–27	4	6	3	—	—	—	—	—	—
99–100.9	Days 19–27	10	8	10	13	1.3	14.5	1.8	12	1.2
101–102.9	Days 19–27	2	0	0	9.5	4.7	0	—	0	—
103–104.9	Days 19–27	0	0	0	0	—	0	—	0	—

TABLE IV

STUDY 1. CLINICAL, VIROLOGICAL, AND SEROLOGICAL FINDINGS AMONG CHILDREN WHO WERE INITIALLY SERONEGATIVE FOR MUMPS AND WHO WERE GIVEN B LEVEL JERYL LYNN STRAIN LOT 137 LIVE MUMPS VIRUS VACCINE OR WHO WERE HELD AS CONTROLS

Case No.	Dose Vol. (ml)	Virus Excretion	Parotid Swelling	Serologic Findings for Mumps at Time Period after Vaccine			
				Neutralization Titer		HI Titer	
				1 mo	6½ mo	1 mo	6½ mo
188	1.0	None	None	32	16	10	5
148	1.0	None	None	32	8	20	5
151	1.0	None	None	16	8	40	20
146	1.0	None	None	16	8	10	5
184	1.0	None	None	8	4	5	5
155	1.0	None	None	8	8	5	5
204	1.0	None	None	8	8	5	<5
153	1.0	None	None	4	4	10	5
181	1.0	None	None	4	4	5	5
154	1.0	None	None	2	2	5	<5
152	1.0	None	None	2	2	5	5
157	1.0	None	None	N.D.	N.D.	10	5
			G.M.:	8	5	8	4
162	0.5	None	None	32	16	40	20
197	0.5	None	None	16	4	10	5
169	0.5	None	None	16	8	10	<5
191	0.5	None	None	16	8	10	5
192	0.5	None	None	16	16	10	5
187	0.5	None	None	8	4	10	5
195	0.5	None	None	8	8	10	5
160	0.5	None	None	8	4	5	5
202	0.5	None	None	8	8	5	5
166	0.5	None	None	4	4	10	10
185	0.5	None	None	2	2	<5	<5
147	0.5	None	None	2	2	10	<5
170	0.5	None	None	2	2	<5	<5
138	0.5	None	None	4	N.D.	5	5
209	0.5	None	None	2	N.D.	40	20
206	0.5	None	None	2	N.D.	<5	<5
150	0.5	None	None	2	N.D.	<5	N.D.
			G.M.:	6	5	8	4
17 Persons (Controls)		None	None	<1	<1	<5	<5

N.D. = Not done.

18-day period among recipients of A level lot 136 vaccine compared with lot 137 recipients and controls, and this difference may have been due to the greater virulence of the level A lot 136 vaccine, since the vaccine caused clinical parotitis in four patients. No other clinically significant findings were observed.

Based on the results obtained, B level Jeryl Lynn strain mumps virus vaccine was selected for further study.

Study 2

Groups of children in the Merna Owens Home who ranged in age from 1½ to 20 years (average, 5 years) were given 1.0 ml

TABLE V

STUDY 2. ORAL TEMPERATURES AMONG MUMPS SERONEGATIVE CHILDREN GIVEN B LEVEL JERYL LYNN STRAIN LIVE MUMPS VIRUS VACCINE LOT 157 COMPARED WITH UNVACCINATED CONTROLS

Maximal Temperature Recorded for the Period (Oral, °F)	Time Period Post-Vaccination	Maximum Temperature Recorded		Total Days of Fever (99° F or >) Recorded; Grouped According to Maximal Temperature for the Period			
				Vaccinees (29 persons)		Controls (17 persons)	
		Vaccinees* (29 persons)	Controls (17 persons)	Total da	Average	Total da	Average
<99	Days 1–4	5	5	—	—	—	—
99–100.9	Days 1–4	24	9	38	1.4	14	1.5
101–102.9	Days 1–4	0	3	0	—	6.5	2.1
103–104.9	Days 1–4	0	0	0	—	—	—
<99	Days 5–12	2	1	—	—	—	—
99–100.9	Days 5–12	24	15	50	2.1	29	2.2
101–102.9	Days 5–12	3	2	8.5	2.8	10	5.5
103–104.9	Days 5–12	0	0	0	—	—	—
<99	Days 13–18	7	5	—	—	—	—
99–100.9	Days 13–18	21	11	31.5	1.5	22.5	2.0
101–102.9	Days 13–18	1	3	4	4	13.5	4.5
103–104.9	Days 13–18	0	0	0	—	0	—
<99	Days 19–28	3	4	—	—	—	—
99–100.9	Days 19–28	25	13	55	2.1	32	2.4
101–102.9	Days 19–28	0	2	0	—	12.5	6.2
103–104.9	Days 19–28	1	0	1	1.0	0	—

* Twelve received 1.0 ml and 17 received 0.5 ml of vaccine.

or 0.5 ml of B level Jeryl Lynn mumps virus vaccine subcutaneously on August 13, 1965. The conduct of the study was as described for Study 1. Twelve children received 1 ml, 17 children received 0.5 ml, and 17 remained as unvaccinated and seronegative controls. Table IV shows that all vaccinated individuals developed neutralizing antibody irrespective of volume of vaccine given and this was not diminished significantly in titer by 4½ months following the initial 28-day sample of blood (total 5½ months). The HI test proved less sensitive than the neutralization test for detecting antibody and a portion of the children failed to reveal any HI antibody response at the lowest serum dilution tested (1:5). As in Study 1, none of the children who received B level vaccine developed parotitis or excreted mumps virus and there was no evidence for transmission of the infection to susceptible children in intimate contact with those who were vaccinated. Further, as shown in Table V, there was no apparent febrile response to the vaccine and none of the vaccinated children showed any other significant clinical manifestation which could be related to the vaccine.

Study 3

Sixty-three children who were initially seronegative for mumps and who ranged in age from 11 months to 12 years (average, 4 years) were given B level Jeryl Lynn live mumps virus vaccine at Lankenau Hospital on March 16, 1966, with parental approval, in viral doses of varying amounts shown in Table VI. Children who initially displayed mumps neutralizing antibody served as controls. It is seen that all children de-

TABLE VI

STUDY 3. TITRATION OF B LEVEL JERYL LYNN STRAIN LIVE MUMPS VIRUS VACCINE LOT 157 IN MUMPS SERONEGATIVE CHILDREN FOR SEROLOGIC RESPONSE

Vaccine*		Number of Persons with Neutralizing Antibody Titer† After Vaccination								Total No.	G.M.‡
Dilution	$TCID_{50}$/Dose	<1	1	2	4	8	16	32	64		
Undiluted	31,700	0	2	0	3	6	2	3	0	16	8
$10^{-0.5}$	10,000	0	2	2	1	4	2	1	0	12	5
$10^{-1.0}$	5,170	0	0	2	2	2	3	2	1	12	10
$10^{-1.5}$	1,000	0	1	2	1	2	2	1	1	10	7
$10^{-2.0}$	317	0	0	2	2	7	1	0	1	13	7

		Number of Persons with Hemagg.-Inhibiting Antibody Titer† After Vaccination									
		<5	5	10	20	40	80	160	320		
Undiluted	31,700	4	11	1	0	0	0	0	0	16	5
$10^{-0.5}$	10,000	5	5	1	0	0	0	0	0	12	4
$10^{-1.0}$	5,170	5	6	3	0	0	0	0	0	12	4
$10^{-1.5}$	1,000	2	7	1	0	0	0	0	0	10	4
$10^{-2.0}$	317	5	6	2	0	0	0	0	0	13	3

* The *in vitro* cell culture infectivity titer of the vaccine was $10^{-4.5}$/1.0 ml.

† Expressed as reciprocal of serum dilution endpoint.

‡ G.M. = Geometric Mean Titer.

veloped neutralizing antibody following mumps vaccine virus in amounts ranging from 31,700 to as little as 317 50% tissue culture infectious doses of virus. The distributions of titer values were roughly the same, irrespective of virus dose. The lower HI antibody titers were apparently due to a lesser sensitivity of this test compared with the neutralization test, and this has been a consistent finding in all studies carried out to date.

As noted in the other two studies, none of the patients who received the B level vaccine developed parotitis or other significant clinical effect and the occurrence of fever (see Table VII) among the vaccinated children was not substantially different from that observed in the controls who were initially immune to mumps and who did not develop antibody.

COMMENT

The findings in the tests indicated that the passage level A of Jeryl Lynn strain live mumps virus vaccine still produced mild parotitis in a small portion of children, and most of the children who displayed evident parotid involvement also showed transient excretion of mumps virus. It was apparent that the level A vaccine was not sufficiently attenuated for routine immunization and, hence, level B vaccine was employed in all further studies.

The B level Jeryl Lynn strain vaccine regularly induced mumps antibody in susceptible children and there was no indication of parotid swelling, virus excretion, febrile or other clinical response, or spread of infection to susceptible contacts. The neutralizing antibody titers achieved following vaccination were substantial and were well retained for at least 7 months. As little as 317 50% tissue culture doses of B level vaccine virus were sufficient to evoke antibody in all children tested.

As reported earlier,[1] the vaccine was dispensed as a dried product which was sufficiently stable on storage in the refrigerator and after rehydration to be practical for routine use. Other papers[2-4] of the pres-

TABLE VII

STUDY 3. ORAL TEMPERATURES AMONG INITIALLY SUSCEPTIBLE CHILDREN WHO RECEIVED GRADED DOSES OF B LEVEL LOT 137 MUMPS VIRUS VACCINE COMPARED WITH THOSE OF CONTROLS WHO WERE IMMUNE PRIOR TO VACCINATION

Maximum Temperature Recorded for the Period Oral °F	Time Period Post-Vaccination	Maximum Temperature Recorded According to Virus Dose $TCID_{50}$					
		31,700 (16 persons)	10,000 (12 persons)	3,170 (12 persons)	1,000 (10 persons)	317 (13 persons)	Initial Immunes (Controls) (26 persons)
"Normal"	Days 1–4	8	0	1	0	3	4
<99	Days 1–4	2	3	2	1	1	0
99–100.9	Days 1–4	7	3	7	7	5	0
101–102.9	Days 1–4	0	1	0	0	2	1
103–104.9	Days 1–4	0	0	0	0	0	1
"Normal"	Days 5–12	4	0	0	0	2	5
<99	Days 5–12	5	5	5	1	2	3
99–100.9	Days 5–12	5	2	5	5	5	11
101–102.9	Days 5–12	0	2	2	2	2	2
103–104.9	Days 5–12	2	0	0	0	2	1
"Normal"	Days 13–18	5	1	2	1	2	4
<99	Days 13–18	5	4	5	5	2	12
99–100.9	Days 13–18	3	2	2	4	7	8
101–102.9	Days 13–18	1	0	1	0	0	0
103–104.9	Days 13–18	0	0	0	0	0	0
"Normal"	Days 19–28	5	1	3	2	3	7
<99	Days 19–28	4	3	5	1	2	8
99–100.9	Days 19–28	3	3	3	5	5	9
101–102.9	Days 19–28	0	0	1	0	1	0
103–104.9	Days 19–28	0	0	0	0	0	0
No record		2	3	2	2	2	2

Vaccination was carried out on March 16, 1966.

ent series record the findings in a controlled study of B level Jeryl Lynn mumps vaccine, which included 1,394 children and which was carried out during 1965 and 1966 in a suburb of Philadelphia. A single dose of the vaccine induced antibody in approximately 98% of more than 400 children who were initially without mumps antibody. Further, the vaccine showed a 97% protective efficacy in 200 vaccinated or control children who were at risk to natural infection in an epidemic of mumps which occurred in the spring of 1966 in the community.

It was apparent that the B level Jeryl Lynn strain live mumps virus vaccine is safe and highly effective and shows great promise as a routine measure for preventing mild as well as serious mumps virus infections.

SUMMARY

Groups of children in institutions who were initially without mumps antibody were inoculated subcutaneously with twelfth chick embryo and chick embryo cell culture passage (level A) or seventeenth passage (level B) Jeryl Lynn strain mumps virus vaccine. All children developed mumps antibody following inoculation of either strain. The level A vaccine, however,

was insufficiently attenuated for routine immunization, since roughly 25% of the vaccine recipients developed parotitis and excreted mumps virus. Children who received B level virus failed to develop fever or parotitis or any other significant clinical reaction to the vaccine and serum amylase values were not significantly altered. Mumps neutralizing antibody persisted for at least 7 months following vaccine B, the longest period tested. A study among children in a community showed that as little as 317 50% tissue culture infectivity doses of virus in level B vaccine induced neutralizing antibody in 100% of children vaccinated. The B level vaccine proved entirely safe and highly effective in inducing protective antibody against mumps.

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Table D.1. Bulk measles live virus vaccine, summary of results of analysis of [redacted] lots. The full release protocols are given in Part IIC, page IIC-85.

Assay	Lot Number [redacted]
CONTROL CELLS	
Homoadsorption	
CONTROL POOL (Test for adventitious agents)	
[redacted]	
Mycoplasma	
Avian Leukosis	
VIRUS HARVEST	
Sterility	
$TCID_{50}$–log_{10}/0.1 mL	
PRECLARIFIED (Test for adventitious ag	
[redacted]	
Sterility	
Mycoplasma	
FINAL BULK	
Identity	
Intact cells	
Sterility	
Protein nitrogen mg/mL	
Potency	
$TCID_{50}$–log_{10}/0.1 mL	
DATE OF RELEASE	

Table D.2a. Bulk mumps live virus vaccine, summary of results of analysis of lot [redacted]. The full release protocols are given in Part IIC, page IIC-92.

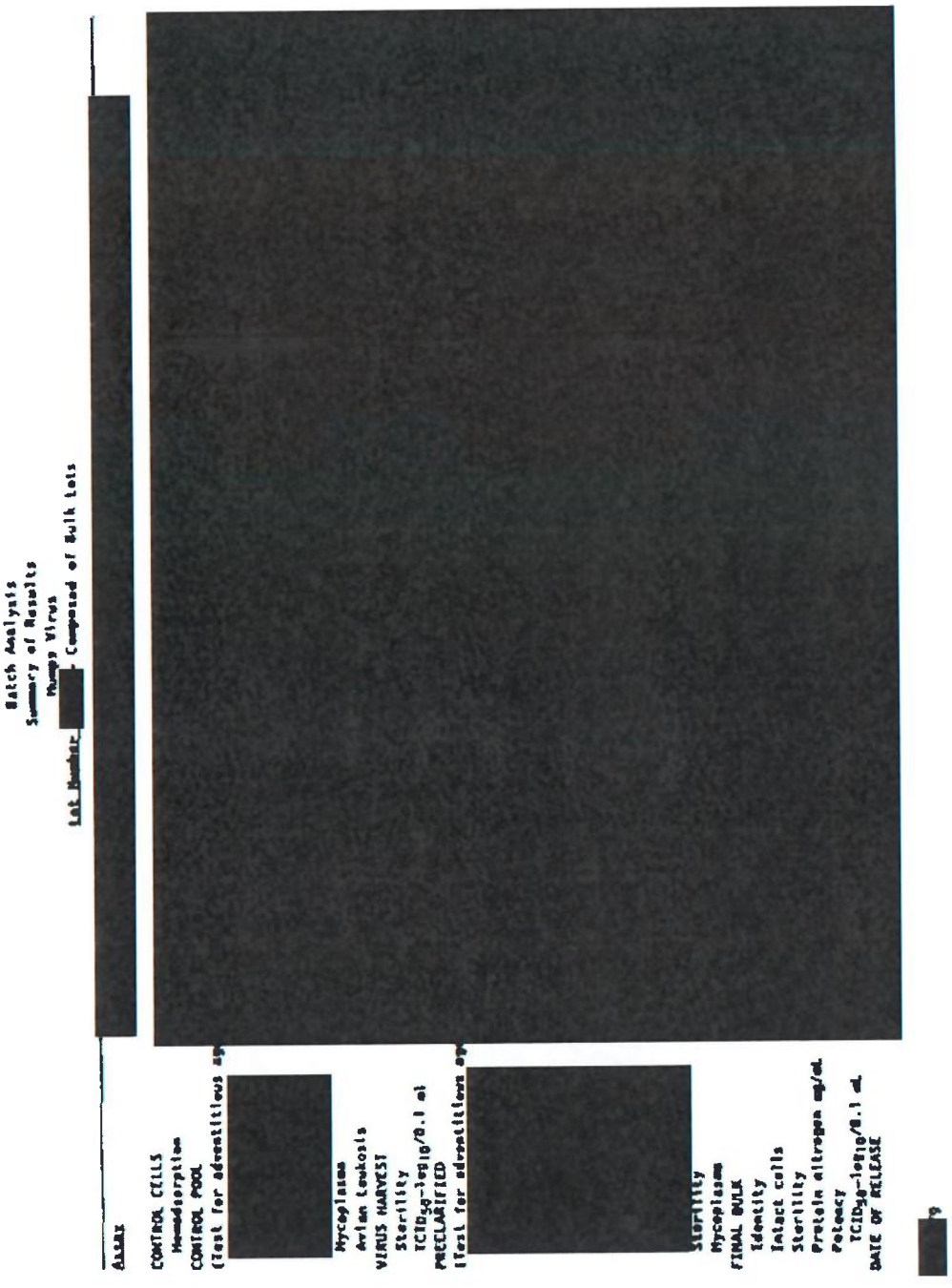


Table D.2b. **Bulk mumps live virus vaccine, summary of results of analysis of lot [redacted] The full release protocols are given in Part IIC, page IIC-92.**

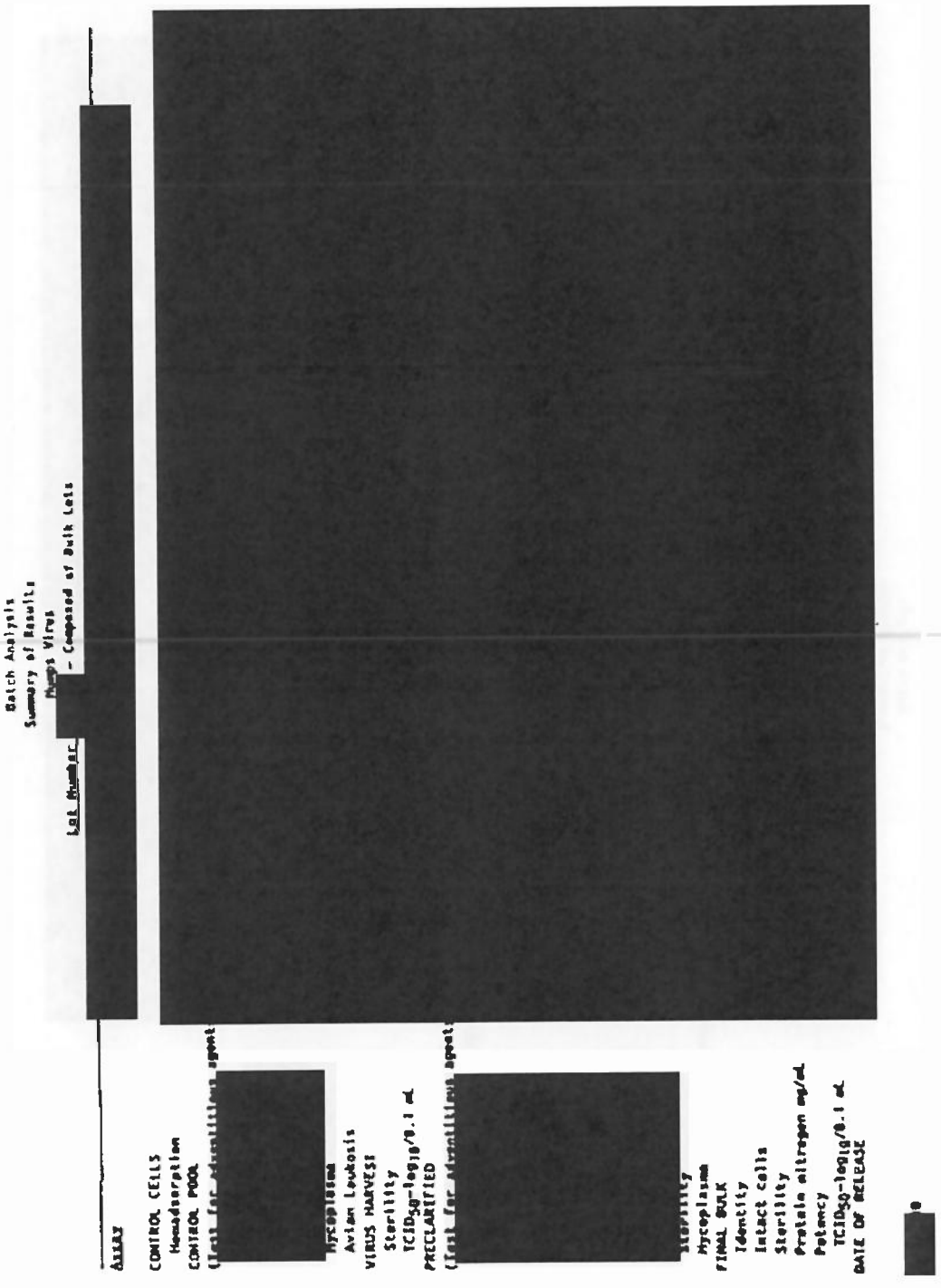


Table D.2c. Bulk mumps live virus vaccine, summary of results of analysis of lot [redacted]. The full release protocols are given in Part IIC, page IIC-92.

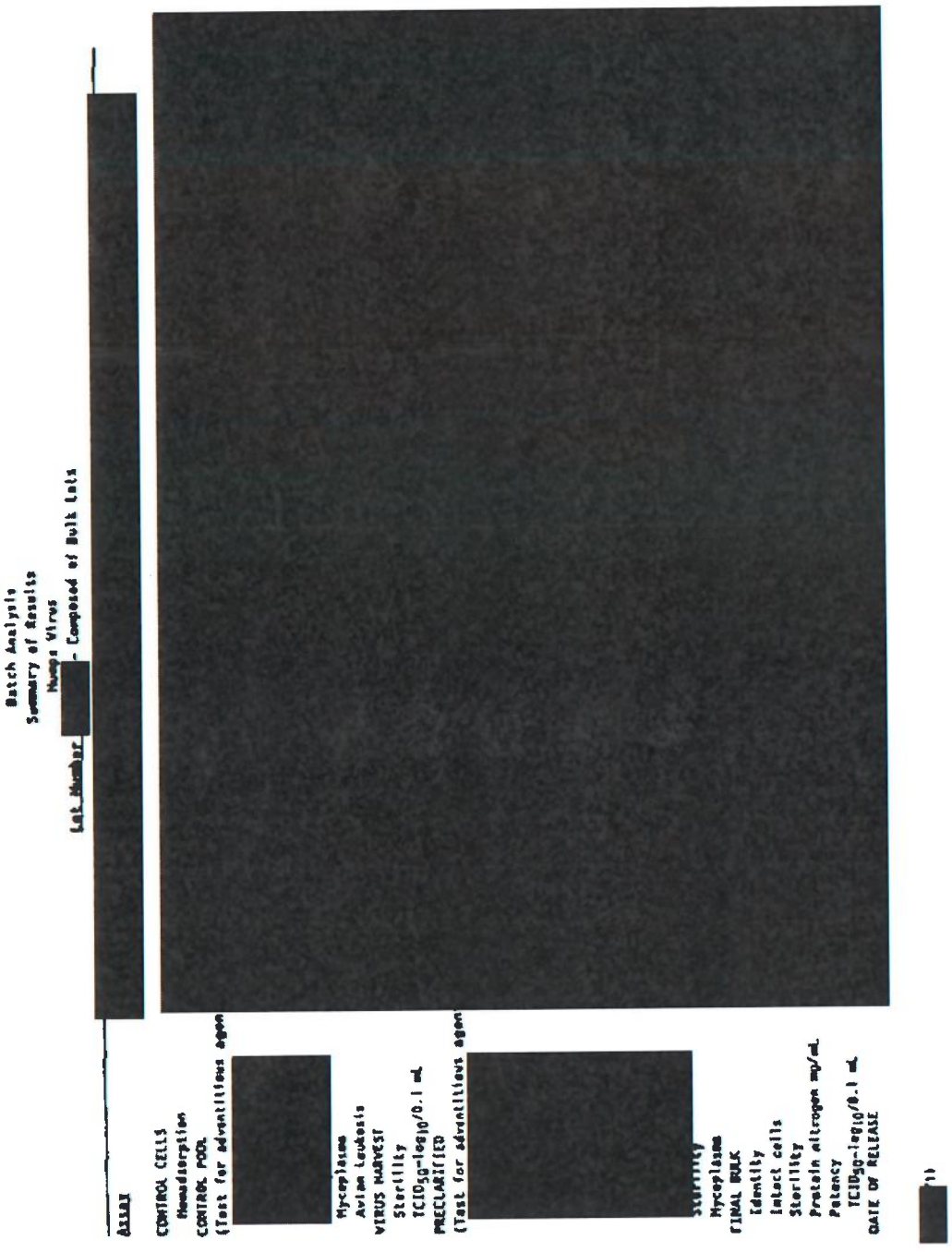


Table D.2d. **Bulk** mumps live virus vaccine, summary of results of analysis of lot [redacted] The full release protocols are given in Part IIC, page IIC-92.

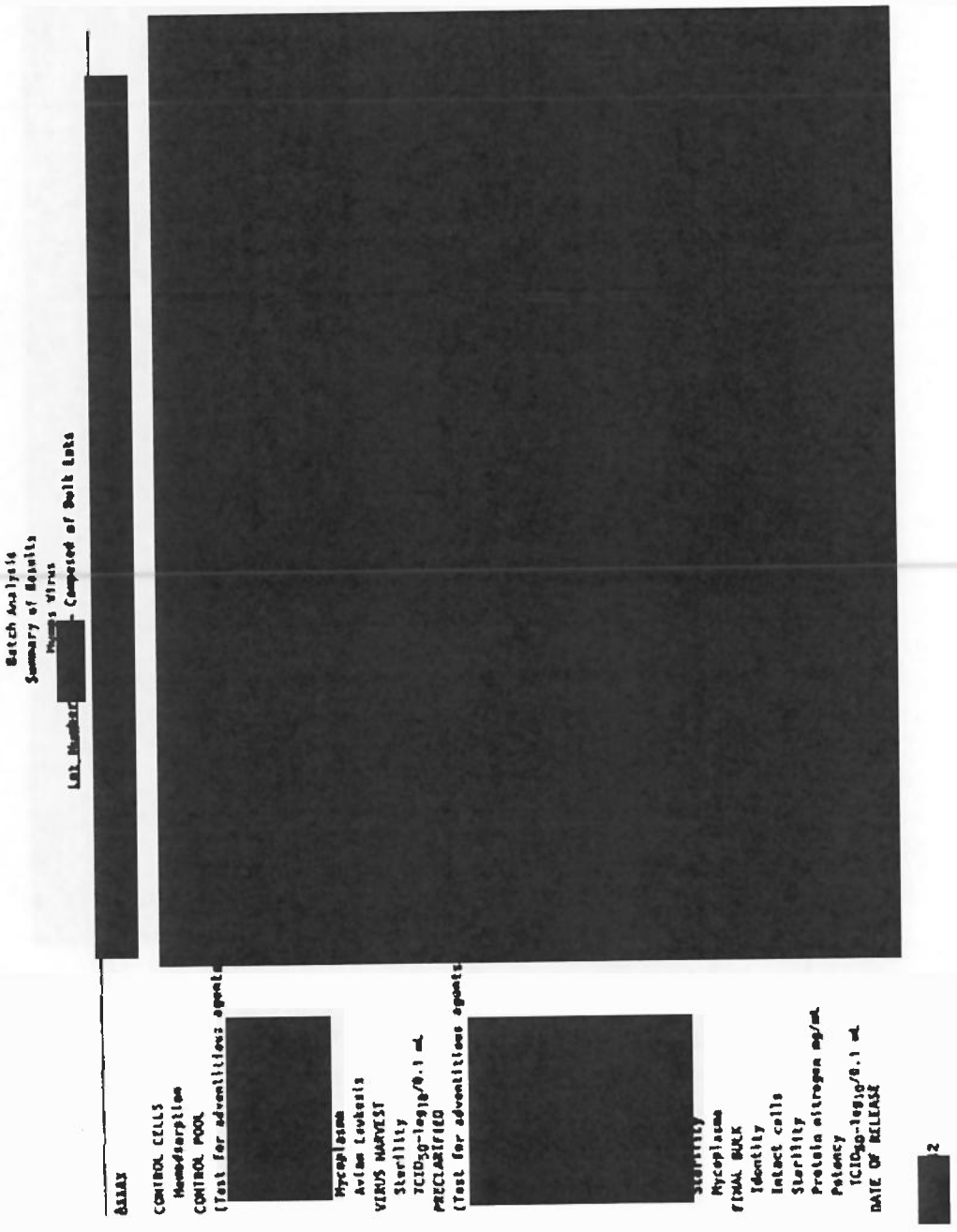


Table D.2e. Bulk mumps live virus vaccine, summary of results of analysis of lot [redacted] The full release protocols are given in Part IIC, page IIC-92.

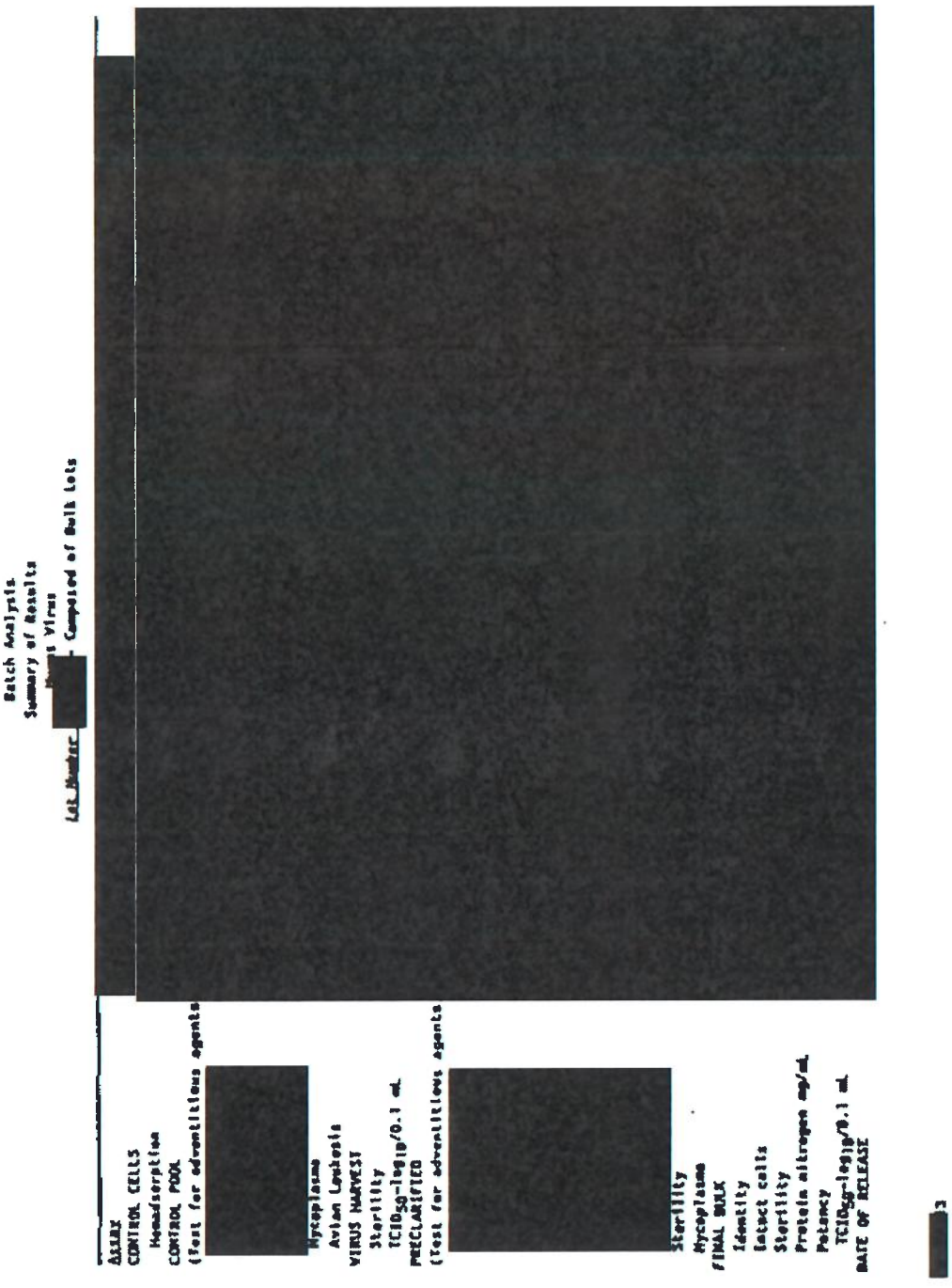


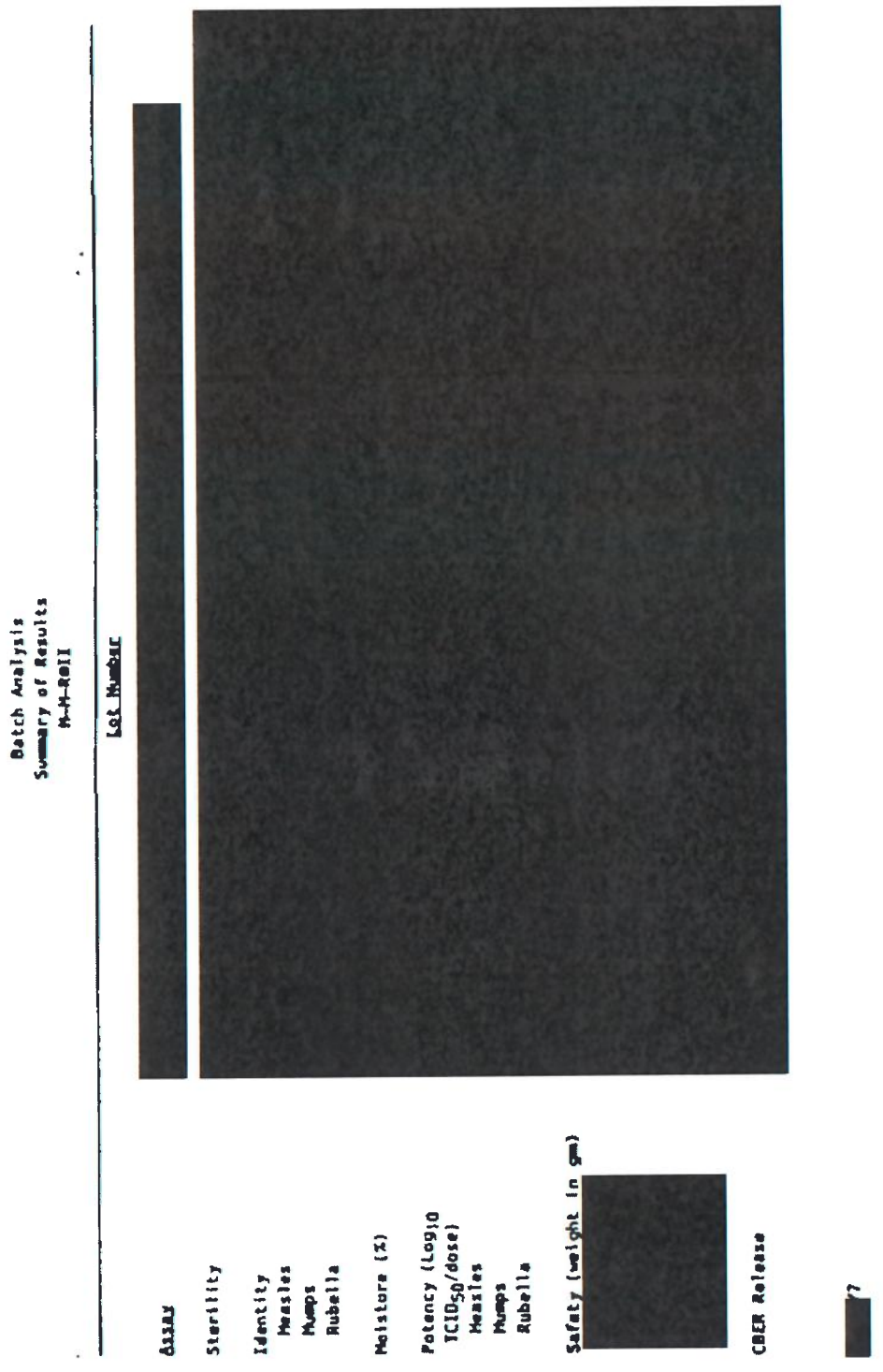
Table D.3. Bulk rubella live virus vaccine, summary of results of analysis of [redacted] lots. The full release protocols are given in Part IIC, page IIC-95.

Batch Analysis
Summary of Results
Rubella Virus
Lot Number [redacted]

Assay	[redacted]
MANUFACTURER'S WORKING CELL BANK	
[redacted]	
Heterotransplantability	
No. of chromosomes	
Chromosome morphology	
Sex	
CONTROL CELLS	
Hemadsorption	
CONTROL POOL	
[redacted]	
Mycoplasma	
VIRUS HARVEST	
Sterility	
$TCID_{50}$-log_{10}/0.1 mL	
PRECLARIFIED	
(Test for adventitious agents)	
[redacted]	
Sterility	
Mycoplasma	
FINAL BULK	
Identity	
Intact cells	
Sterility	
$TCID_{50}$-log_{10}/0.1 mL	
DATE OF RELEASE	

[redacted]14

Table E.1. **Final measles, mumps and rubella live virus vaccine, summary of results of analysis of [redacted] lots. The full release protocols are given in Part IIE, page IIE-13**



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Extension Directives 89/342 and 89/381 EEC

M-M-R®II

Measles, Mumps and Rubella Vaccine, Live, MSD

C

Expert Report on the

Clinical Documentation

By: [redacted]

Merck Research Laboratories
West Point, Pennsylvania, 19486, USA

March 26, 1993

The documentation in this volume also supports the monovalent vaccines;

ATTENUVAX® (Measles Vaccine, Live, MSD)
MUMPSVAX® (Mumps Vaccine, Live, MSD)
MERUVAX®II (Rubella Vaccine, Live, MSD)

and bivalent combinations of these vaccines;

BIAVAX®II (Rubella and Mumps Vaccine, Live, MSD)
M-M-VAX® (Measles and Mumps Vaccine, Live, MSD)
M-R-VAX®II (Measles and Rubella Vaccine, Live, MSD)

1. SUMMARY OF PRODUCT CHARACTERISTICS

a) Type of application

The application is for the relicensing, under the implementation of Extension Directives 89/342 EEC and 89/381 EEC, of a product which is already licensed and on the market in the member state where this application is made.

b) Composition.

The vaccine is a triple antigen containing (1) **ATTENUVAX®** (Measles Virus Vaccine, Live), a more attenuated line of measles virus derived from Enders' attenuated Edmonston B strain and grown in cell cultures of chick embryo; (2) **MUMPSVAX®** (Mumps Virus Vaccine, Live), the Jeryl Lynn (B level) strain of mumps virus grown in cell cultures of chick embryo; and (3) **MERUVAX®II** (Rubella Virus Vaccine, Live), the Wistar RA27/3 strain of live attenuated rubella virus grown in human diploid cell (WI 38) culture.

The reconstituted vaccine is for subcutaneous administration. When reconstituted as directed, the dose for injection is 0.5 mL and contains not less than the equivalent of 1,000 $TCID_{50}$ (tissue culture infectious doses) of the U.S. Reference Measles Virus; 20,000 $TCID_{50}$ of the U.S. Reference Mumps Virus; and 1,000 $TCID_{50}$ of the U.S. Reference Rubella Virus. Each dose contains approximately [redacted] of neomycin. The product contains no preservative. Sorbitol and hydrolyzed gelatin are added as stabilizers. A6

c) Indications

For simultaneous immunization against measles, mumps and rubella in persons 15 months of age and older.

d) Precautions

Adequate treatment provisions, including adrenalin, should be available for immediate use should an anaphylactic or anaphylactoid reaction occur. Due caution should be employed in administration of M-M-R®II in persons with a history of cerebral injury, individual or family histories of convulsions, or any other condition in which stress due to fever should be avoided. The physician should be alert to the temperature elevations which may occur following vaccination. Children and young adults who are known to be infected with human immunodeficiency viruses but without clinical manifestations of immunosuppression may be vaccinated; however the vaccinees should be monitored closely for vaccinee-preventable diseases because immunization may be less effective than for uninfected persons.

Vaccination should be deferred for at least 3 months following blood or plasma transfusions, or administration of human immune serum globulin. Excretion of small amounts of the live attenuated rubella virus from the nose or throat has occurred in the majority of susceptible individuals 7-28 days after vaccination. There is no confirmed evidence to indicate that such virus is transmitted to susceptible persons who are in contact with the vaccinated individuals. Consequently, transmission through close personal contact, while accepted as a theoretical possibility, is not regarded as a significant risk.

There are no reports of transmission of the live measles or mumps viruses from vaccinees to susceptible contacts.

It has been reported that live attenuated measles, mumps and rubella virus vaccines given individually may result in a temporary depression of tuberculin skin sensitivity. Therefore if a tuberculin test is to be done, it should be administered either before or simultaneously with M-M-R®II. Children under treatment for tuberculosis have not experienced exacerbation of the disease when immunized with live measles virus vaccine; no studies have been reported to date of the effect of live measles virus vaccines on untreated tuberculous children. As for any vaccine, vaccination with M-M-R®II may not result in seroconversion in 100% of susceptible persons given the vaccine.

Pregnancy

Animal reproduction studies have not been conducted with M-M-R®II. It is also not known whether M-M-R®II can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore the vaccine should not be administered to pregnant females; furthermore, pregnancy should be avoided for three months following vaccination.

Nursing mothers.

It is not known whether measles or mumps vaccine virus is secreted in human milk. Recent studies have shown that lactating post-partum women immunized with live attenuated rubella vaccine may secrete the virus in breast milk and transmit it to breast-fed infants. In the infants with serological evidence of rubella infection none exhibited severe disease; however, one exhibited mild clinical illness typical of acquired rubella. Caution should be exercised when M-M-R®II is administered to a nursing woman.

e) Marketing/post-marketing

M-M-R®II was first licensed in the United States of America on September 15, 1978, and is now licensed in more than 30 countries, worldwide. During the period 1978 to 1992, over [redacted] doses of this vaccine have been supplied worldwide.

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M-M-R® II

2. CLINICAL EXPERT OPINION – TABLE OF CONTENTS

M-M-R®II, Measles, Mumps and Rubella Vaccine

Part IV, Documentation on Clinical Studies

2. EXPERT REPORT

1. Introduction

Of the 3 childhood diseases measles, mumps, and rubella, measles carries the highest rate of mortality. At least 1.6 million children die each year from measles [1]*. In the United States, in the years preceding the introduction of specific vaccination (1963), 500 deaths were attributed annually to measles [2]. The practice of vaccination in developed countries brought about a sharp decrease in the incidence of these diseases.

The reduction in measles and mumps incidence which followed wide spread use of the respective vaccines was paralleled by a reduction of over 99% in disease specific morbidity and mortality and rates of complication including measles encephalitis, mumps meningitis, orchitis and deafness.

The rubella epidemic occurring in the United States in the years preceding the widespread usage of the vaccine (1964-65) was responsible for 20,000 cases of congenital rubella. During 1979, the mumps virus was responsible for over 1000 hospitalizations in England, primarily from meningitis [3].

The prospect of the eradication of these 3 disease has been made possible only by the development of specific protective vaccines and the widespread usage of the vaccines.

1.2. Interest in a New Anti-Measles, Mumps, Rubella Vaccine and Presentation of the Report

Licensure of the trivalent vaccine, M-M-R® II (**) the subject of this report, should permit an increase in the number of children vaccinated against measles, mumps, and rubella. It could contribute to lowering the incidence of these three diseases, widening the prospects for their eventual eradication.

This report describes the chronology of the development of monovalent anti-measles, mumps, rubella vaccines, and of bi- and trivalent vaccines. It details the clinical tests conducted before and after market production of M-M-R® II vaccine. The analysis of vaccine effectiveness and tolerability closes the report.

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* Publications noted above and in following pages, will be found in Part IV, Book 4

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2. Development of Monovalent Anti-Measles, Mumps, Rubella Vaccines

2.a. Measles

The measles virus was isolated for the first time in cell culture in 1954; this strain (Enders) was utilized in the development of two vaccines approved in the United States of America in 1963: an inactivated vaccine and an attenuated vaccine (Edmonston B strain). The inactivated vaccine was abandoned in 1967 on account of its weak protective capacity and because vaccinated children developed atypical cases of measles when exposed to the wild virus. The attenuated vaccine was usually administered with gammaglobulin in order to diminish the intensity of adverse post-vaccination reactions. Two other more-attenuated live vaccines (Schwartz and Merck) were derived from the Edmonston B strain by additional passages in cell culture, and were marketed in the United States in 1965 and 1968 respectively.

The further Edmonston B strain developed at the Merck Institute for Therapeutic Research differs from the original Edmonston B strain in that it is passaged through cell culture at [redacted]:

[redacted]

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The further attenuated Edmonston B strain was chosen for the monovalent anti-measles vaccine, (ATTENUVAX®)approved in the United States on March 21, 1968 (*); this strain constitutes the measles component of both the bivalent (*) and the trivalent vaccine M-M-R®, and was maintained in M-M-R® II vaccine.

2.b. Mumps

The Jeryl Lynn strain was isolated by research workers at the Merck Institute for Therapeutic Research from a throat culture taken on March 20, 1966 from a patient with mumps. The strain was attenuated by [redacted] passes on the amniotic membrane of an embryonic egg and [redacted] passage in chicken cells in order to obtain the seed strain. The strain utilized in making the vaccines undergoes several additional passes. The Jeryl Lynn type B strain was chosen for the monovalent mumps vaccine (MUMPSVAX®), which was approved in the United States December 28, 1967. This strain constitutes the mumps component of the bivalent vaccines and the trivalent vaccine (M-M-R® and M-M-R® II).

2.c. Rubella

The anti-rubella vaccine, derived from the HPV-77 Duck Embryo strain (HPV-77 DE), was approved in the United States on June 9, 1969. This strain was used in M-M-R® vaccine, but due to its poorer immunogenicity, it was replaced by the Wistar RA 27/3 strain in the M-M-R® II combination.

(*) Live measles-mumps vaccine, live rubella-mumps vaccine (Merck & Co.)

The Wistar RA 27/3 strain was isolated in 1964 from a culture from a fetus infected by rubella virus. After inoculation and an initial series of passages on human diploid cells at low temperature, a second series of passages was completed to attenuate the strain, thus constituting the base strain. In the same manner as for the mumps strains, the strain utilized in making the vaccines undergoes several additional passes. The Wistar RA 27/3 strain has been licensed in the United States since September 18, 1978 as MERUVAX® and is the only monovalent rubella vaccine available. This strain constitutes the rubella constituent of bivalent vaccines (*) and of the trivalent vaccine M-M-R® II.

3. M-M-R® Trivalent Measles, Mumps, Rubella Vaccine

The first clinical trials conducted with the trivalent vaccine [4,5,6] combining the further Edmonston B, Jeryl Lynn, and HPV-77 DE strains took place in 1967 and revealed the following characteristics:

3.a. Immunogenicity

The criteria for seroconversion were an anti-measles antibody titer: ≥1/5, an anti-mumps titer: ≥1/1, and an anti-rubella titer: ≥1/8 by hemagglutination inhibition assay.

The result of the immunogenicity studies indicate that 93%-100% of the vaccinated children in seven clinical trials (n=715) demonstrated seroconversion against measles. These figures varied from 91% to 99% (mumps) and from 89% to 100% (rubella) [Table 1*][5]. The comparison between the immunogenicity the trivalent vaccine and that of the three monovalent vaccines produced no evidence of a significant difference in the observed immune responses, demonstrating the absence of any interference with the immune response by any component of the combination vaccine [Table 2][5].

3.b. Tolerability

The frequency of fever occurring in the vaccinated population (n=228) in the 28 days following the vaccination was greater than that observed in a non vaccinated, control population (n=106); nevertheless, the tolerability was acceptable. In a smaller study, at least 50% of the children reported no adverse reactions over the entire length of the study [Table 3 and 4)[5].

3.c. Persistence of Antibodies after Vaccination

The persistence of antibodies was studied within a population vaccinated 3, 5, and 7 years previously with the trivalent vaccine and compared to the antibody level measured 6 weeks after vaccination [7,8,9]. Seven and one-half years after vaccination, the anti-measles antibody level was equivalent to the initial level, while the anti-rubella and anti-mumps antibody levels were greater than those observed following vaccination—presumably a result of subclinical reinfections in the immune vaccinees [14].

(*) See Tables 1 to 14 following page 16 of this expert report.

This variation over a course of time is similar to the variation of anti-measles, anti-mumps, and anti-rubella antibodies observed in the years following vaccination with each of the monovalent vaccines. These comprehensive results supported the licensing of the M-M-R® vaccine in the United States April 22, 1971.

3.d. Lower Immunogenicity of Anti-Rubella Vaccine (HPV-77 DE Strain)

However, other studies showed that a certain percentage of children vaccinated 4, 5, and 6 years previously with either the monovalent vaccine or the M-M-R® vaccine displayed a lack of antibodies against rubella (36%), against measles (18%), and to a lesser extent against mumps [Table 5][10]. The rubella HPV-77 DE strain induced an immune response quantitatively and qualitatively inferior to that observed during natural infections. It did not bring about the appearance of secretory antibodies, and no anamnestic reaction was observed after revaccination, thus not allowing for maintenance of protectability levels in postpubertal women. Finally, the poor tolerability profile of HPV-77 DE strain limited its use [11]. These findings led the development of a more highly immunogenic and better tolerated rubella strain.

4. M-M-R® II Trivalent Measles, Mumps, Rubella Vaccine: Adoption of the RA 27/3 Rubella Virus Strain and Results of Clinical Tests Conducted before Introduction to the Market

4.a. Choice of a New Rubella Vaccine Strain

The essential difference between M-M-R® and M-M-R® II vaccines arose from the introduction of the rubella Wistar RA27/3 strain to replace the HPV-77 DE strain. The RA 27/3 strain, isolated in 1964, cultivated on human diploid cells (WI-38), and attenuated by successive passages, permits the production of a level of antibodies higher than that observed with the HPV-77 DE strain, [Table 6][11].

These results were confirmed or supplemented by other studies [12,13]. Furthermore, tests which placed subjects vaccinated with various vaccines in contact with wild virus revealed that the rate of infection was lower in the group vaccinated with RA 27/3 than in groups vaccinated with other strains [14].

Finally, the persistence of antibodies, measured three years after vaccination in 17 children, showed a reduction of the antibody concentration limited to two dilutions [11].

4.b. Comparison of the Immunogenicity and the Tolerance of M-M-R® and M-M-R® II Vaccines.

From 1975 to 1977, seven studies were conducted comparing the immunogenic properties and the tolerability of different combinations of vaccine (*).

- Studies 442 and 443 were conducted to study the immunogenicity and the clinical tolerability of M-M-R® vaccines in comparison to monovalent RA 27/3 vaccine (Study 442 and 443) and bivalent containing RA 27/3 + Edmonston B measles strain (Study 442).
- Studies 453, 467 and 484 compared the immunogenicity of M-M-R® vaccines (with the HPV-77 DE strain) and M-M-R® II (with the RA 27/3 strain); in addition, comparisons of monovalent vaccines and a placebo were carried out in Study 453.
- Studies 511 and 513 compared the immunogenicity and the tolerance of different lots of M-M-R® II vaccines.

* See study summaries 1 through 7 in Part IV, Clinical Documentation, Book 1, Section D

Materials and Methods

All the studies were conducted with children less than 15 years of age (mean age ~2 years) vaccinated by a single injection; a blood sample was taken at the time of injection and then 6 to 8 weeks later. The criteria for seroconversion were satisfied if the level of antibodies for measles was ≥1/5, for mumps ≥1/1 or 1/2 (depending on the study), and for rubella ≥1/2 by hemagglutination inhibition.

The tolerability profile of the vaccines was also assessed.

Results

Study 442 (number = 199 children):

The method of administration of the RA 27/3 strain – alone, in combination with the measles strain, or with the measles plus mumps strains – did not diminish immunogenicity. The measles constituent retains the same immunogenicity (>92% seroconversion) in any combination. The tolerability of the monovalent vaccine is equivalent to the tolerability of the two vaccine combinations.

Study 443 (number = 105 children) :

This published [15] study confirmed the previous results in showing that the RA 27/3 strain, alone or in combination, induced yearly 100% seroconversion. Tolerability was comparable to that observed in Study 442.

Study 459 (number=309 children):

The comparison of two monovalent rubella vaccines, triple combinations including one or another of them (M-M-R® and M-M-R® II), and monovalent measles and mumps vaccines, shows that the combination of these different constituents caused no attenuation of the immune response. In fact, the preliminary results (n=135) revealed no significant difference between the levels of antibodies observed 6 weeks after the various vaccinations [Tables 7]. The definitive results based on findings from 308 children (n=135) [Table 8] were published [16] and confirmed the absence of interaction between the different constituents of the M-M-R® II vaccine compared to the responses seen after individual administration of these same constituents [Table 9].

Study 467 (number = 137 children) :

The levels of anti-rubella antibodies observed after vaccination with M-M-R® II vaccine are greater than those observed after vaccination with the M-M-R® vaccine; the levels of anti-measles antibodies are comparable.

Study #484 : (number = 155 children entered the study) :

This study was conducted to compare responses to combined live measles-mumps-rubella virus vaccine containing either the HPV-77 DE or RA 27/3 strain as the rubella component. Of the 77 children who were followed up, seroconversion was observed in 30/31 (98%) of children receiving HPV-77 DE vaccine and in 47/47 (100%) of children receiving RA 27/3 vaccine.

Study 511 (number = 150 children) and Study 513 (number = 175 children):

Studies 511 and 513 demonstrated a sustained high level of seroconversion (80%-100%) against the 3 antigen constituents resulting from 3 different lots of vaccine. There was no evidence of significant difference in immunogenicity between the lots. The tolerability was acceptable for all lots utilized; as these tests are based on findings from a large number of children (325) and from 3 different lots of vaccines. Tolerability will be discussed in detail in the section on tolerability (IV B.6)

Analysis of these 7 studies showed that the mean rate of seroconversion, calculated from results of 864 vaccinated children, were 95% for measles, 96% for mumps, and 99% for rubella [Table 10] [15].

These results justified the modification of the composition of the vaccine (substituting RA 27/3 strain in place of HPV-77-DE strain, retaining the other strains), which was licensed in the United States September 15, 1978. The market production of all vaccines – mono-, bi-, or trivalent – containing the HPV-77-DE strain was halted in favor of the monovalent RA 27/3 strain or bivalent vaccines combining this strain with others; M-M-R® was no longer available after this date and was replaced by the M-M-R® II vaccine containing the RA 27/3 component.

5. M-M-R® II Trivalent Measles, Mumps, Rubella Vaccine: Studies Conducted after Introduction onto the Market

Since the introduction to the market of MMR® II vaccine, numerous studies have added to the earlier findings; these studies deal with the immunogenicity, indications and usage in special cases, vaccine effectiveness, and the causes of vaccine failure observed since introduction to the market. Lastly, of tolerability of the vaccine has been significantly expanded by the analysis of adverse experience report based on the utilization of tens of millions of doses.

5.a. Studies on the Immunogenicity and Tolerability of M-M-R® II Vaccine

- Seven studies were conducted in different countries between 1980 and 1985; these studies reported equivalent rates of seroconversion [Table 11][17].
- The high level of tolerability of the vaccine was verified in studies utilizing 4 different lots of vaccine [18].

5.b. Persistence of Antibodies after Vaccination

The persistence of antibodies 2 years after vaccination in 19 children was comparable to that observed with the M-M-R® vaccine [15]. From this similarity, one can extrapolate that the persistence of antibodies beyond this 2-year period would be equivalent to that already observed after vaccination with the M-M-R® vaccine.

5.c. Influence of Age on the Immune Response to the Vaccine

The rate of seroconversion against the different antigens varies with the specific antigen and with the age of the subject. The measles and rubella vaccines are more immunogenic

in 15 month-old children than they are in 12-month-olds [19]; more importantly, the percentage of vaccinated children having post vaccination antibody levels <1/4 increases sharply if the vaccination is done before the age of 12 months [20].

5.d. Importance of Reimmunization with the Anti-Measles Vaccine for Children Vaccinated before the Age of 15 Months

There appears to be an anamnestic response when a second injection of anti-measles vaccine is given to 15 month-old children who were first vaccinated at the age of 9 months [21] since there is no IgM response and there is a sharp anamnestic type of increase in the level of antibodies after the second injection. The magnitude of the immune response observed after reimmunization is not affected by the age (7-12 months) at which the initial injection was administered [22].

5.e. Effect of the Simultaneous Administration of the M-M-R® II Vaccine with the Diphtheria, Tetanus, Pertussis and Oral Poliovirus Vaccines

As reported by Deforest *et al.*, [23] the safety and efficacy of simultaneous administration of measles-mumps-rubella (M-M-R® II), diphtheria-tetanus-pertussis (DTP) and trivalent oral poliovirus (OPV) vaccines in a test group of 405 children were compared with the safety and efficacy of sequential administration of the same vaccines in a control group of 410 children given M-M-R® II followed by booster doses of DTP and OPV 2 months later. The study was double blind and placebo controlled with respect to DTP and OPV. Seroconversion rates to measles, mumps and rubella exceeded 96% in both groups. Geometric mean titers to measles ($P = 0.05$) and rubella ($P = 0.004$) were higher in the test group and titers of antibodies to the other seven antigens were similar in both groups. Clinical reaction data were analyzed in 248 of 405 test children and 249 of 410 control children. The rates of serious vaccine-associated reactions were low and similar in the two groups. Some minor side effects were reported more frequently in the test group, but these differences were judged to be related to study design rather than to differences in the safety of the two vaccine schedules. The results indicate that the safety and serologic efficacy of administering M-M-R® II simultaneously with reinforcing doses of DTP and OPV in the second year of life is equivalent to the safety and efficacy observed after administering these antigens separately. [Table 13] [23].

5.f. Vaccination of Children with Allergies

Since the measles and mumps constituents of the vaccine are derived from chicken egg cell cultures, there is a risk that an immediate hypersensitive reaction could be provoked in subjects having a history of anaphylactic reactions to egg proteins. It is recommended that the vaccine be administered to this type of patient only after administering cutaneous tests using the diluted vaccine [24]. Several clinical studies confirmed the nature of the response in the cutaneous tests [24,25,26]. The utility of cutaneous tests was also verified in cases involving subjects with atopic allergies, subjects with asthma, and subjects with prior cow's milk allergy or history of anaphylaxis after vaccination [27].

5.g. Vaccination and Pregnancy

Since the RA 27/3 strain was approved in the United States in 1974, there have been 635 reported cases in which women were vaccinated with the RA 27/3 strain in the three months preceding pregnancy or in the weeks following conception. The baby's condition at birth was documented; none of the 522 live births had any abnormalities compatible with congenital rubella syndrome; 20 cases ended in abortion or premature birth; 54 therapeutic abortions were reported; and 42 cases were not documented [Table 14] [28]. The risk of congenital rubella syndrome over the duration of this study was 0%, in comparison to a risk of 20% in a non immunized population having rubella during the first trimester of pregnancy.

5.h. Protective Efficacy of M-M-R® II Vaccine

The protective efficacy of the vaccine must be judged essentially on the protection it induces against the disease in consideration. It can be assessed by the measure of incidence of this disease on a national level as a result of requirement of reporting of new cases with the health authorities. The protection can also be estimated by the measure of its effectiveness during an epidemic.

Measles

In the United States, the incidence of measles has diminished by 99.8% from 1950-1962 (the period preceding the introduction of the first measles vaccine) to 1983. During this time the number of cases reported annually declined from 315 per 100,000 persons to 0.6 per 100,000 persons [2]. The number of related deaths and cases of acute encephalitis have similarly declined [2]. The number of cases of subacute sclerosing panencephalitis gradually declined almost to zero beginning several years later [2]. The vaccine effectiveness observed during an epidemic remained high in children vaccinated at the age of 15 months or older [29].

During the period 1963-1982, 18.9 million doses of vaccine containing Edmonston B strain and 117.7 million doses of vaccine containing the more attenuated measles virus (ATTENUVAX®) were distributed in the United States Note that ATTENUVAX® has been the only monovalent measles vaccine available in the United States since 1976.

In Sweden, a double vaccination schedule with M-M-R® II (first dose at 18 months, booster at age 12) was introduced in 1982. The annual incidence of measles fell accordingly from 76 cases per 100,000 persons in 1982 to 1.2 cases per 100,000 in 1988 [30]. This decrease must be attributed to the M-M-R® II vaccine (known as VIRIVAC® in Sweden), as it has been the only anti-measles, mumps, rubella vaccine available there since 1982.

In Finland, a double vaccination with the M-M-R® II vaccine permitted a 93% decrease in the number of measles cases between 1982 and 1985 [31]. In this country as well, the only anti-measles, mumps, rubella vaccine is the M-M-R® II vaccine.

Mumps

The Jeryl Lynn strain of the M-M-R® II vaccine caused a sharp decrease in the number of many cases reported in the United States [32], Sweden [30], and Finland. Furthermore, analysis of two epidemics [33-34] occurring within selected communities demonstrated the high level of protection offered by the vaccine 75% [34]. Neither the formulation of the vaccine (monovalent or trivalent), the age of the subject at the time of vaccination, nor the year or month of vaccination had any negative influence on the reduction of disease in this population [33].

Rubella

In the United States, cases of rubella decreased by 98% from 1966-68 to 1990; this decrease began following the introduction of rubella vaccination. The incidence of congenital rubella syndrome experienced a similar decline. The introduction of rubella vaccine appeared to check the epidemics which has been commonplace in this century [34]. In Sweden and Finland, the utilization of the trivalent vaccine permitted a sharp reduction in the cases of rubella. In the latter country, the incidence of the disease decreased by 87% from 1982 to 1985 [31].

Change in the number of cases of viral encephalitis after the widespread usage of the vaccination.

The decrease in the number of registered cases of acute encephalitis linked to the three viruses constitutes another means of judging the effectiveness of the vaccine; using this measure it was observed that the disappearance of cases of acute encephalitis attributable to the three viruses occurred rapidly after the introduction of the trivalent vaccine

5.i. Failure of Vaccination

Causes of apparent vaccination failures during the recent recrudescence in the measles incidence in the United States has been studied [36]. Most cases (71.3%) occurred in non-vaccinated subjects, whereas 28.6% of the cases were subjects vaccinated with a live measles vaccine before age 1. These failures can be explained by the vaccine's lack of immunogenicity when given to children young enough to have detected persistent maternal antibodies which can block successful vaccination. Analyses of cases occurring in vaccinees compared to controls revealed a number of risk factors for vaccine failure: vaccination before the age of 15 months and vaccination before March 1, 1979 (42). The correlation between the occurrence of vaccine failures and vaccination at too early an age (<15 months) was verified in other studies [37,38,39,40,41]. Serological analysis in vaccinated subjects at the time of an epidemic showed a differentiation between primary vaccine failure (appearance of type IgM antibodies at the time of measles, demonstrating the absence of initial post-vaccination seroconversion) and secondary failures (exclusive seroconversion of type IgG after clinical measles, indicating an earlier post-vaccination seroconversion); the primary failures appeared more commonly than the secondary failures and were associated with more severe clinical symptoms [42].

5.j. Development of Schedules for Vaccination

Taking into account the difficulty of assuring protection for an entire population exposed to only a single injection of vaccine, various authorities in charge of establishing vaccination schedules have proposed a second injection of the measles, mumps, rubella vaccine in order to seroconvert any individual with primary vaccine failure and to boost immunity in those with waned titers. In the United States, the Advisory Committee For Immunization Practices (ACIP) recommends that the first injection be given after 15 months of age with the second given between ages 4 and 6 years [43]. The American Academy of Pediatrics recommends that the booster be given between ages 11 years and 12 years of age [44]. As noted above, Sweden recommends that the second injection be given at the age of 12 years, while in Finland the recommended age for the booster is 6 years of age [45,31].

6. M-M-R® II Trivalent Measles, Mumps, Rubella Vaccine: Tolerability Study

The analysis of tolerability was based on adverse reactions:

- observed during clinical studies conducted before introduction to the market,
- and made known to Merck & Co., after introduction of the vaccine to the market.

6.a. Adverse Reactions Occurring During Studies Conducted Before Market Production

The tolerability of the M-M-R® II vaccine was studied in the course of 7 clinical studies conducted before placing it on the market. Adverse reactions occurring in the 42 days following vaccination during Studies 511 and 513 conducted with three different lots of vaccines in 325 children are summarized below:

Results

Occurrence of Post-Vaccination Febrile Reaction

Less than half of the vaccinated children had a temperature >37.2°C during the observation period. The occurrence of febrile reaction was not affected by the presence nor the absence of specific antibodies at the time of vaccination, nor by the lot of vaccine utilized. The number of children having a temperature >37.2°C reaches its maximum between the 5th and 12th days following the vaccination as is expected with the monovalent live measles vaccine.

Occurrence of Local and General Symptoms

Local reactions are occurring in 7.3% of cases and are chiefly transient and mild. The general adverse reactions reported most frequently are irritability (2%-23.1% according to the lot of vaccine and the time period includes upper respiratory tract infection (9.1% to 34.5%) or gastroenteritis (3% to 30.3%). Morbilliform-type rashes occur in 1.8%-11.4% of patients between the 5th and 12th day after vaccination.

The vaccine is generally well-tolerated; the adverse reactions expected between the 5th and 12th day are infrequent and well-tolerated. In addition, the cases of upper respiratory tract infection and gastroenteritis may also have been provoked by intercurrent bacterial or viral infections which occur frequently at that age. The long period of observation (42 days) no doubt increased this phenomenon.

6.b. Adverse Reactions occurring after introduction to the market

In August 1992, an internal analysis was conducted on the worldwide rates of spontaneous adverse experience reporting to Merck & Co., since first introduction of the trivalent vaccine, M-M-R® II on to the market in 1978. The result of this review is given in Part IV, Book 2.

Approximately [redacted] doses of M-M-R® II vaccine have been sold in the domestic and international markets as of August 31, 1992. It is estimated that about [redacted] doses have been administered.

The conclusions from this analysis are:

An evaluation of adverse experiences reported to Merck & Co., Inc. indicates that M-M-R® II is generally well tolerated with few serious vaccine-related adverse experiences reported, considering the vast number of doses sold.

Only six adverse events had spontaneous, voluntary reporting rates of greater than one case per million doses administered. These adverse events include rash (4.32), fever (3.95), systemic reaction (1.28) and febrile convulsions (1.03). Misuse (3.95) and lack of response (3.13) were also reported at a rate greater than one case per million doses distributed.

The total crude rate of reported occurrence of encephalitis and meningitis and meningitis adverse events report after M-M-R® II is 1.1 per million doses administered. This reporting rate includes reported cases and possible cases based on a review of reported selective neurologic adverse events.

The rate of reported deaths is 0.3 per million doses administered. The four most common causes of death were encephalitis (8), unknown cause (8), Sudden Infant Death Syndrome (5), bacterial infection (4).

Abstracts from all publications received during the reporting period are provided as an Annotated Bibliography for M-M-R® II in Part IV, Book 3.

7. Countries in Which the M-M-R® II Vaccine is Marketed (*)

M-M-R® II vaccine is authorized for marketing in over 30 countries (including 11 members of the European Community) and is marketed under name M-M-R® II or under another commercial name.

(*) Please see page 16

8. Conclusions and Recommendations

Conclusions:

1. M-M-R® II vaccine is a trivalent vaccine intended to protect against measles, mumps, and rubella; it is composed of the Merck further attenuated line of the Edmonstan B strain (measles), the Jeryl Lynn (mumps) strain, and the RA 27/3 (rubella) strain.

2. The comparison of M-M-R® and M-M-R® II vaccines and each of the individual vaccines demonstrates that M-M-R® II is as immunogenic for measles and mumps as M-M-R® vaccine and the monovalent vaccines. The introduction of the RA 27/3 strain permits M-M-R® II vaccine to induce the appearance of higher levels of antibodies against rubella virus than those measured after vaccination with M-M-R® vaccine.

3. The practical conditions for the use of M-M-R® II vaccine (combination with other approved vaccines) are known and permit such usage

4. The vaccine is highly effective. Studies conducted during epidemics of measles and mumps show that the protective efficacy of M-M-R® II is high. Furthermore, M-M-R® II has brought about a very sharp decrease in the incidence of these three diseases in countries where the level of vaccination is high. Eradication of these three diseases is thus conceivable; the decrease of the incidence of the diseases in the United States, Sweden, and Finland is solely attributable to M-M-R® II since M-M-R® II is the only measles, mumps, rubella vaccine available in these countries.

5. The increase of the incidence of measles during the 1980s is first of all linked to a remaining group of non vaccinated children, to vaccination at too early an age, and finally, to the existence of children who do not respond well to vaccines.

6. In order to increase the percentage of persons vaccinated, various countries are proposing to add a booster injection in addition to the initial injection in the vaccination schedule. This booster injection should be administered before 12 years of age.

7. The vaccine is well-tolerated and the reported adverse reactions are rare in light of the [redacted] of doses already administered. A16

Recommendations:

M-M-R® II vaccine is indicated for simultaneous immunization against measles, mumps, and rubella. The proposed schedule for administration should take into account the national schedule for vaccination in present use and the knowledge available from the analysis of vaccination failures.

Vaccination consists of one injection of M-M-R® II vaccine given after the age of 12 months.

However:

- It is advised that the vaccination of children with low exposure (for example, children not living in a closed community) be deferred until the age of 15 months, as children vaccinated at 15 months have a lower risk of vaccine failure.
- The vaccine may be administered simultaneously with diphtheria, tetanus, pertussis, DTP and oral poliovirus vaccines by injecting at 2 separate sites.
- Children vaccinated with the monovalent measles vaccine between the ages of 9 and 12 months should receive an injection of the M-M-R® II vaccine at the age of 15 months.
- Children initially vaccinated with the trivalent measles, mumps, rubella vaccine between the ages of 12 and 15 months should be reimmunized by 12 years of age.

[redacted]

C

[redacted]

M-M-R®II, Measles, Mumps and Rubella Vaccine
Part IV, Documentation on Clinical Studies

M-M-R®II - Worldwide Marketing Authorizations

Country	Original Registration date	Registration No.
Australia	Feb 9 1989	88/6103
Austria		
Bahrain	Nov 30 1986	494/86
Belgium	Feb 1 1984	922 IS 108 F 17
Brazil	Mar 3 1980	1306/80
Canada	May 7 1979	9427-M18-299
Chile	Jun 27 1980	1958/79
Colombia	Nov 24 1982	005871
Costa Rica	Feb 8 1979	1005-BV-4070
Denmark	Mar 26 1986	
Ecuador	Sep 30 1985	14.511-1
Egypt	Oct 28 1979	16280
Finland	Aug 1982	No approval system
Germany	Jan 29 1980	10.485
Greece	Jan 15 1982	A6A/14391/81/E.63
Hong Kong	Oct 27 1978	HK-01891
India	Feb 26 1983	12-32/78-DC
Indonesia	Jun 01 1992	DKI9263600444A1
Ireland	May 8 1984	PA 35/39/2
Israel	Dec 27 1989	
Luxembourg	Jul 3 1984	483/91/05/2097
Netherlands	Oct 16 1981	57/38-B1
New Zealand	May 17 1990	
Norway	May 1992	
Philippines	Jun 30 1979	BR40-79-5
Saudi Arabia	Apr 4 1987	7/20/85
Spain	Oct 28 1983	3.162
Sweden	Feb 5 1982	9757
Switzerland	Aug 9 1979	268/79
Thailand	Jun 5 1980	393/2523
United Kingdom	Sep 1 1987	PL/0025/0078
United States	Sep 15 1978	Ref: 77-303
Venezuela	Mar 23 1981	P.B. 675

March 26, 1993

Merck Research Laboratories
Name of Product: M-M-R® II
Active ingredients: Measles, mumps, rubella vaccine, live

Summary of Clinical Studies
Clinical Documentation, Book 1
Comparison of mono- b- and trivalent vaccines
containing RA 27/3 or HPV-77 DE rubella strain

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Summary of Clinical Tests of Combined Live Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

Investigator	Lot No.	Age Range	Age Mean (Yrs.)	No. Vacc.	Antibody Responses among Triple Seronegatives: Measles No. Conv./ No. Seroneg. (%)	Measles GMT	Mumps No. Conv./ No. Seroneg. (%)	Mumps GMT	RA 27/3 Rubella No. Conv./ No. Seroneg. (%)	RA 27/3 Rubella GMT	Ref.
Villarejo	[redacted]	10m- 7y	3.7	199	23/23 (100)	99	22/23 (96)	7	23/23 (100)	149	1
Weibel	[redacted]	11m- 8y	1.7	105	65/69 (94)	56	66/69 (96)	8	69/69 (100)	133	2
Lerman	[redacted]	14m- 4y	1.5	59	13/14 (93)	62	13/14 (93)	17	14/14 (100)	269	3
Weibel	[redacted]	11m- 7y	1.9	137	55/58 (95)	71	57/58 (98)	7	58/58 (100)	146	4
Gershon	[redacted]	13m-15y		39							5
Villarejo	[redacted]	8m-11y	3.3	50	9/11 (82)	20	10/11 (91)	5	11/11 (100)	226	6
	[redacted]	11m- 7y	3.3	50	4/5 (80)	25	4/5 (80)	11	5/5 (100)	169	
	[redacted]	11m-11y	4.2	50	2/2 (100)	28	2/2 (100)	8	2/2 (100)	256	
Weibel	[redacted]	12m- 7y	1.6	58	30/32 (94)	74	30/32 (94)	16	32/32 (100)	250	7
	[redacted]	12m- 4y	1.6	58	35/36 (97)	72	35/36 (97)	23	35/36 (97)	307	
	[redacted]	11m- 4y	1.5	59	33/34 (97)	66	33/34 (97)	27	33/34 (97)	256	
	Totals			864	269/284 (95)	63	272/284 (96)	11	282/284 (99)	179	

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This table conatins the same information as Table 10, referred to on page 7 of the expert report. and summarizes the clinical study rogram conducted between 1975 and 1978

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TABLE I

Serologic Response in Triple Seronegative Children Given Four Lots of Trivalent Vaccine

Study Location	Vaccine Lot No.	Antibody Responses											
		Measles (HI)				Mumps (Neut)				Rubella (HI)			
		Conversion		Titer		Conversion		Titer		Conversion		Titer	
		Rate	%	Range	GM	Rate	%	Range	GM	Rate	%	Range	GM
Pilot study													
Havertown-Springfield	[redacted]	30/30	100	5-320	38.2	29/30	97	<1-64	6.5	30/30	100	8-256	30.6
Field studies													
Suburban Philadelphia		74/82	90	<5-640	54.4	80/82	98	<1-64	7.9	73/82	89	<8-512	30.4
Suburban Philadelphia		71/76	93	<5-640	57.8	75/76	99	<1-64	6.8	74/76	97	<8-512	45.7
Suburban Philadelphia		69/70	99	<5-2,560	73.0	67/70	96	<1-64	6.4	66/70	94	<8-256	28.4
Costa Rica-San Salvador		149/155	96	<5-320	33.1	144/155	93	<1-64	6.3	149/155	96	<8-128	32.7
Costa Rica-San Salvador		138/145	95	<5-320	28.6	132/145	91	<1-128	7.3	135/145	94	<8-128	23.5
Costa Rica-San Salvador		153/157	97	<4-256	30.5	153/157	97	<1-64	6.6	143/157	91	<8-256	19.8
Total (all lots)		684/715	96	<4-2,560	38.5	690/715	96	<1-128	6.8	670/715	94	<8-512	27.8

*HI signifies hemagglutination-inhibition test; neut, neutralization test; GM, geometric mean titer.

from J.Stokes *et al.* J. Am. Med. Assoc. *218* (1):57-61,1971 [5]

TABLE 2

Antibody Responses Among Initially Seronegative Children Vaccinated With Trivalent Compared With Monovalent Vaccines

Study No.	Vaccine	Vaccinates			Level of Antibody Response*					
					Measles (HI)		Mumps (Neut)		Rubella (HI)	
		No.	Age Range	Mean Age, yr	Titer Range	GMT	Titer Range	GMT	Titer Range	GMT
232	Combined measles-mumps-rubella	24	11 mo-3 yr	1.4	8-320	98.1	1-128	18.1	8-512	52.8
87[5]	Merieux measles	25	11 mo-4 yr	2.2	20-640	80.6				
71[4]	Jeryl Lynn mumps	25	2-5 yr	4.5			2-256	8.7		
183[3]	Rubella (HVP-77 + S Dust)	25	11 mo-5 yr	1.8					8-256	60.8

*GMT signifies reciprocal of geometric mean antibody titer; HI, hemagglutination-inhibition; neut, serum neutralization.

from J.Stokes *et al.* J. Am. Med. Assoc. *218* (1):57-61,1971 [5]

TABLE 3

Miscellaneous Complaints After Vaccination Among 30 Children (Pilot Study)

Complaint	Days Following Vaccination, No. (%)			
	1-4	5-12	13-18	19-28
Upper respiratory tract illness	8 (26.7)	9 (30.0)	5 (16.7)	3 (10.0)
Otitis				1 (3.3)
Gastroenteritis	1 (3.3)	2 (6.7)		
Rash (heat and diaper	1 (3.3)	2 (6.7)	2 (6.7)	1 (3.3)
Irritability	2 (6.7)	3 (10.0)	2 (6.7)	
Teething		2 (6.7)	1 (3.3)	
No complaint	19 (63.3)	15 (50.0)	21 (70.0)	25 (83.3)

from J.Stokes *et al.* J. Am. Med. Assoc. *218* (1):57-61,1971 [5]

TABLE 4

Occurrence of Fever at Critical Time Period (Days 5-12) Among Vaccinated Children and Controls*				
Maximum Temperature Orally	Vaccinated Children (228)		Control Children (106)	
	No.	%	No.	%
<99 F	108	47.1	57	58.8
99-100.9 F	86	38.6	36	37.1
101-102.9 F	26	11.7	3	3.1
103-104.9 F (39.4–40.5 C)	6	2.7	1	1.0
Not taken	5		9	

*Three lots of trivalent vaccine used in suburban Philadelphia.

from J.Stokes *et al.* J. Am. Med. Assoc. *218* (1):57-61,1971 [5]

TABLE 5

Immune Status of Vaccinees at Follow-up						
		Subjects With Serum Antibodies		Postvaccination Time Tested, yr		
Vaccine	Subjects Tested	Present*	Absent (%)	Range	Mean	Median
Rubella	159	101	58 (36)	0.3-9	4.7	4.5
Measles	168	137	31 (18)	1-14	6.5	5.0
Mumps	141	128	13 (9)	0.7-8	4.5	4.0

*Rubella hemagglutination-inhibiting (HI) titer ≥8; measles HI titer ≥2; mumps neutralizing titer ≥2.

From Balfour *et al.*, Am. J. Dis. Child. *132*:573-577, 1978 [10]

TABLE 6

Complement-Fixation Responses to Rubella Vaccines			
Vaccine	Percent Seroconverting*	Geometric Mean Titer	Geometric Mean Titer of Seroconverters†
HPV-77-DE	73	3.3	4.2 (16)
RA27/3 subcutaneously	100	6.0	6.0 (27)
RA27/3 intranasally	91	6.8	8.0 (22)

*Eight weeks immunization.
†Number in parentheses is number of seroconverters.

† measured by complement fixation

From Plotkin *et al.*, J. Am. Med. Assoc. *225* (6):585-590, 1973 [11]

TABLE 7

Seroconversions and Geometric Mean Titers for Children
Who Were Initially Seronegative Prior to Vaccination (Study #459)

	Age		Measles	Mumps	Rubella
Vaccine	Range	Mean	No. Conv./Total (GMT)	No. Conv./Total (GMT)	No. Conv./Total (GMT)
ATTENUVAX	14m - 3y	1.5	6/6 (90)		
MUMPSVAX	14m - 4y	1.7		11/12 (12)	
RUBELLA (HPV-77)	14m - 2y	1.4			6/7 (95)
RUBELLA (RA 27/3)	14m - 4y	1.6			11/11 (199)
M-M-R (HPV-77)	14m - 4y	1.5	20/20 (77)	20/20 (14)	20/20 (111)
M-M-R (RA 27/3)	14m - 4y	1.6	13/14 (62)	13/14 (17)	14/14 (269)

Statistical nonparametric comparison shows no suppression of post-vaccination antibody titer of any component when administered in combined form with rubella RA 27/3 or HPV-77.

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from Summary of Clinical Investigative Studies, Ref. 3, Study #459, Table 1. (Section D, Clinical Documentation, Book 1)

TABLE 8

DEVELOPMENT OF ANTIBODY IN INITIALLY SERONEGATIVE CHILDREN SIX WEEKS FOLLOWING ADMINISTRATION OF PLACEBO OR VACCINE

		MEASLES		MUMPS		RUBELLA	
Placebo/vaccine	No. Paired Sera	%*	GMT†	%	GMT	%	GMT
PLACEBO	23	0	—	5	6	0	—
MEASLES	23	100	82	—	—	—	—
MUMPS	33	—	—	92	19	—	—
RUBELLA HPV-77-DE-5	0	—	—	—	—	95	296‡
MEASLES-MUMPS-RUBELLA (HPV-77 : DE-5)	85	99	77	89	15‡	99	144‡
RA 27/3 RUBELLA	33	—	—	—	—	100	306
MEASLES-MUMPS-RUBELLA (RA 27/3)	91	96	89	90	31‡	100	301

from Lerman *et al.* Pediatr. *68* (1):18-22, 1981[16]

* : percent of those who develop a detectable antibody

† : geometric mean titer of those who became seropositive

‡ : $p < 0,05$ for mumps GMTs with measles-mumps-rubella (HPV-77:DE-5) vs measles-mumps-rubella (RA 27/3) and for rubella GMTs with HPV-77:DE-5 rubella vs measles-mumps-rubella (HPV-77:DE-5)

TABLE 9

PROPORTION (%) OF CHILDREN WHO EXPERIENCED SYMPTOMS AND SIGNS DURING SIX WEEKS FOLLOWING ADMINISTRATION OF PLACEBO OR VACCINE

			FEVER (°F)						
Placebo/vaccine	No.	Local Reaction*	101-102.9 °F	103-104.9 °F	Respiratory Symptoms	Rash†	Lymph-adenopathy	Sore Eyes	Joint Symptoms
PLACEBO	42	7	24	0	74	9	0	9	0
MEASLES	43	2	28	5	79	12	2	14	0
MUMPS	41	14	15	7	63	2	5	19	0
RUBELLA HPV-77-DE-5	47	6	13	6	66	13	4	17	0
MEASLES-MUMPS-RUBELLA (HPV-77 : DE-5)	142	5	22	8	68	17	4	17	0.7
RUBELLA RA 27/3	46	4	24	4	67	11	4	17	0
MEASLES-MUMPS-RUBELLA (RA 27/3)	141	8	25	11	72	20	8	16	0.7

* : pain, redness, or swelling at the injection site on days 0 to 4
† : non-specific erythematous maculopapular rash involving two or more areas of the body

TABLE 10

Summary of Clinical Tests of Combined Live
Measles-Mumps-Rubella (RA 27/3) Virus Vaccine

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Study No.	Investigator	Lot No.	Age Range	Age Mean (Yrs.)	No. Vacc.	Antibody Responses among Triple Seronegatives: Measles No. Conv./ No. Seroneg. (%)	Measles GMT	Mumps No. Conv./ No. Seroneg. (%)	Mumps GMT	RA 27/3 Rubella No. Conv./ No. Seroneg. (%)	RA 27/3 Rubella GMT	Ref.
442	Villarejos	[redacted]	10m- 7y	3.7	199	23/23 (100)	99	22/23 (96)	7	23/23 (100)	149	1
443	Weibel		11m- 8y	1.7	105	65/69 (94)	56	66/69 (96)	8	69/69 (100)	133	2
459	Lerman		14m- 4y	1.5	59	13/14 (93)	62	13/14 (93)	17	14/14 (100)	269	3
467	Weibel		11m- 7y	1.9	137	55/58 (95)	71	57/58 (98)	7	58/58 (100)	146	4
484	Gershon		13m-15y		39							5
511	Villarejos		8m-11y	3.3	50	9/11 (82)	20	10/11 (91)	5	11/11 (100)	226	6
			11m- 7y	3.3	50	4/5 (80)	25	4/5 (80)	11	5/5 (100)	169	
			11m-11y	4.2	50	2/2 (100)	28	2/2 (100)	8	2/2 (100)	256	
513	Weibel		12m- 7y	1.6	58	30/32 (94)	74	30/32 (94)	16	32/32 (100)	250	7
			12m- 4y	1.6	58	35/36 (97)	72	35/36 (97)	23	35/36 (97)	307	
			11m- 4y	1.5	59	33/34 (97)	66	33/34 (97)	27	33/34 (97)	256	
		Totals			864	269/284 (95)	63	272/284 (96)	11	282/284 (99)	179	

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from Summary of Clinical Investigative Studies, (Section D, Clinical Documentation, Book 1)

TABLE 11

Rate of seroconversion in studies on combined, trivalent measles–mumps–rubella vaccine

HI = haemagglutination inhibition. NI = neutralisation test. HIG = haemolys in gel. IMM = immunofluorescent assay. ind. imm = indirect immunofluorescent assay. HAI = microhaemagglutination inhibition assay. EHI = enhanced haemagglutination inhibition. ELISA = enzyme-linked immunosorbent assay

		Seroconversion in % for						
		Measles		Mumps		Rubella		
Author	Year	%	Test-method	%	Test-method	%	Test-method	
Weibel	1980	95	HI	96	NT	99	HI	Same components as M-M-R II
Lerman	1981	96	HI	90	ind. imm	100	HI	
Bottiger	1982	90–100	HIG	90–100	HIG	90–100	HIG	
Christenson	1983	96	HI	93	NT HIG	99	HIG	
Böttiger	1985	82	HIG	50	HIG	100	HIG	
Vesikari	1984	100	HI	98	EHI	100	HI	
Just	1985	98	HI	100	IMM	100	HI	
Weibel	1980	Persist.	HI	Persist.	NT	Persist.	HI	Other MMR vaccine
Balfour	1978	?	HI	?	NT	?	HI	
Khanjanasthiti	1978	?	HI	<40	HI	<40	HI	
Buynak	1969	100	HI	93	NT	100	HI	
Borgono	1973	100	HI	96	NT	96	HI	
Stokes	1971	96	HI	95	NT	94	HI	
Isozaki	1982	98	HI	57	NT	98	HI	
Sugiura	1982	97	?	65	?	100	?	
Krugman	1977	96	HI	90	NT	94	HI	
Brunell	1983	98	ELISA	98	ELISA	97	HAI	

From Fahgren *et al.*, Scand. J. Soc. Med. *16*:129-135, 1988. [17]
? = not known
Persist = "persistence of immunity" [after 7½ years]

TABLE 12

Children With Positive Reactions for Antibody at Various Levels Approximately 60 Days After Administration of Measles-Mumps-Rubella Vaccine and Reinforcement Doses of Diphtheria-Tetanus-Pertussis and Oral Poliovirus Vaccines

Antigen	Antibody Titer	% Positive	
		Control Group (n = 391–398)	Test Group (n = 385)
Measles	≥10	96.0	97.7
Mumps	≥80	98.5	97.7
Rubella	≥8	100.0	100.0
Pertussis	≥16*	98.0	97.7
	≥64*	84.1	86.0
	≥128*	65.2	71.2
Diphtheria	≥0.10 IU/mL†	100.0	99.7
Tetanus	≥0.01 IU/mL‡	100.0	100.0
Polio 1	≥0.1 IU/mL	98.7	99.2
Polio 2	≥0.1 IU/mL	100.0	100.0
Polio 3	≥0.1 IU/mL	98.5	98.2

* Data for more than one level of antibody to pertussis are given because no agglutinating titer has been established as a minimal protective level. Protective antibodies for pertussis probably make up only a small portion of the agglutinating antibodies[30] and protection has been demonstrated in the absence of agglutinins.[31] The level of protection is said to approach 100% at macroagglutination titers ≥320 (usually about double microagglutination titers) and to be about 63% at macroagglutination titers <10 following immunization.[32,33]

† Most authorities consider a diphtheria antitoxin titer of 0.01 IU/mL to represent a minimal level and a titer of 0.10 IU/mL a protective level.[30]

‡ Universally considered to be a protective level.[30]

From Deforest *et al.*, Pediatr. *81* (2):237-246, 1988 [23]

TABLE 13

Reported Reactions During the First 48 Hours Following Diphtheria-Tetanus-Pertussis-Oral Poliovirus (DTP/OPV) Vaccine Administered Simultaneously With or Separately From Measles-Mumps-Rubella (MMR) Vaccine*

	DTP/OPV Placebo With MMR (day 0) (n = 249)	DTP OPV Placebo Without MMR (day 60) (n = 248)	DTP/OPV Without MMR (day 60) (n = 249)	DTP OPV With MMR (day 0) (n = 248)	P Value†
Reaction at DTP or placebo injection site (left arm)					
Redness					
<5.1 cm (2 in)	11 (4.4)	13 (5.2)	124 (49.8)	120 (48.4)	.8
≥5.1 cm (2 in)	0	0	36 (14.5)	52 (21.0)	.06
Swelling					
< 5.1 cm (2 in)	9 (3.6)	14 (5.6)	123 (49.4)	131 (52.8)	.4
≥ 5.1 cm (2 in)	0	1 (0.4)	25 (10.0)	34 (13.7)	.2
Pain					
Mild/moderate	17 (6.8)	18 (7.3)	135 (54.2)	133 (53.6)	.9
Severe	0	2 (0.8)	50 (20.1)	59 (23.8)	.3
Systemic reaction					
Rectal temperature (°C)					
38.3–39.4	21 (8.4)	22 (8.9)	88 (35.3)	105 (42.3)	.1
>39.4	1 (0.4)	2 (0.8)	11 (4.4)	4 (1.6)	.07
Drowsiness or sleepiness	12 (4.8)	8 (3.3)	35 (14.1)	59 (23.8)	.006
Fretfulness	28 (11.2)	26 (10.6)	121 (48.8)	130 (52.4)	.4
Prolonged crying	2 (0.8)	0	2 (0.8)	6 (2.4)	.2
High pitched, unusual cry	0	0	2 (0.8)	0	.2
Convulsions	0	0	1 (0.4)	1 (0.4)	1.0
Hypotonic hyporesponsive episode	0	0	0	0	1.0

* Results are numbers (%) of children.

† *P* values by χ^2 analysis are results of comparison between those given DTP/OPV with and without MMR.

From Deforest *et al.*, Pediatr. *81* (2):237-246, 1988 [23]

TABLE 14

Pregnancy outcomes for 635 recipients of RA 27/3 vaccine — United States, January 1979-December 1986

Prevaccination Immunity Status	Total Women	Live Births	Spontaneous Abortions and Stillbirths	Induced Abortions	Outcome Unknown
Susceptible	224	172 *	11	30	13
Immune	32	30	1	0	1
Unknown	379	320 †	8	24	28
Total	635	522	20	54	42

*Includes two twin births.
†Includes one twin birth.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES / PUBLIC HEALTH SERVICE

From MMWR, 457-461, July 24, 1987. [28]

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3. INFORMATION ON THE AUTHOR

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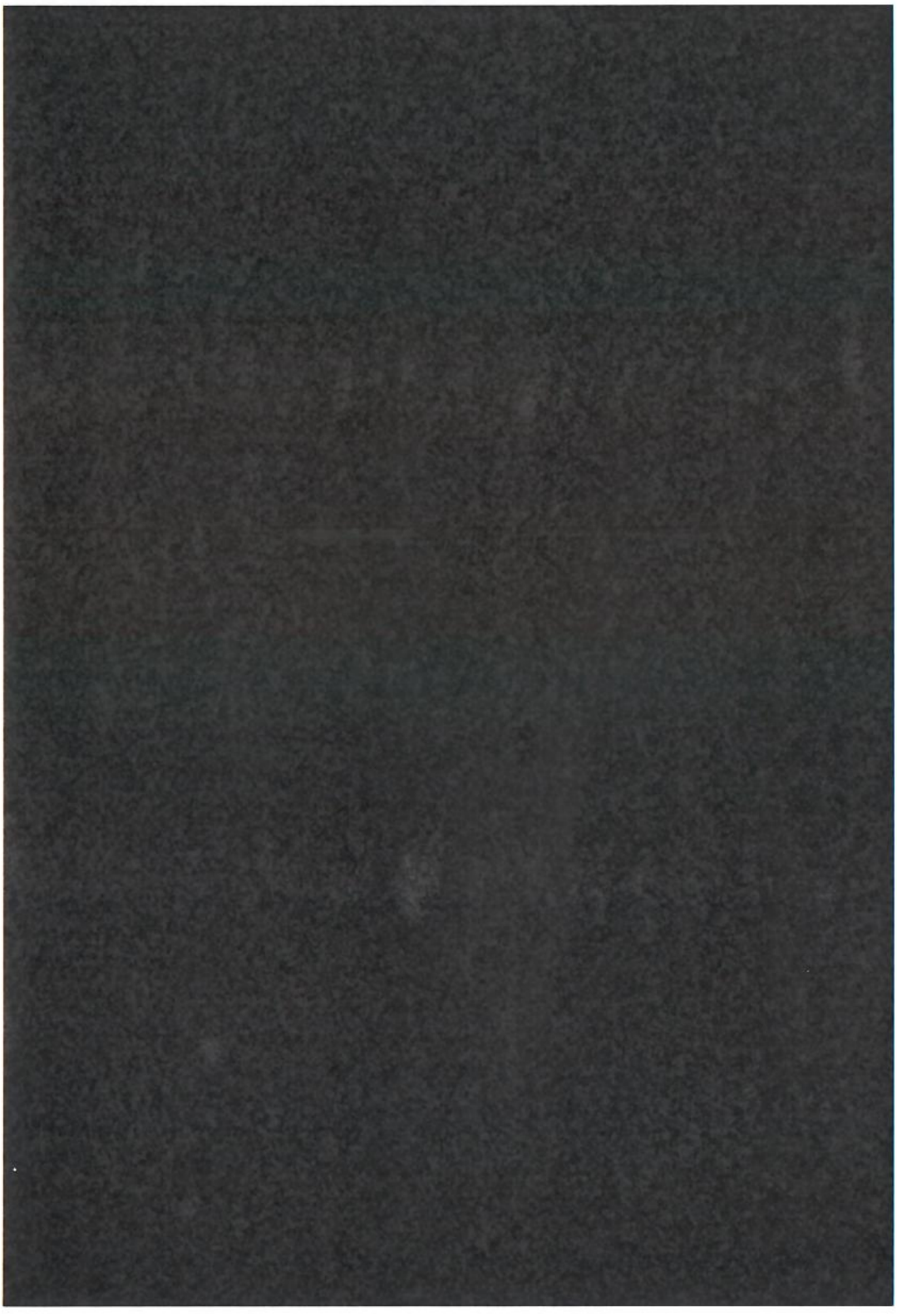

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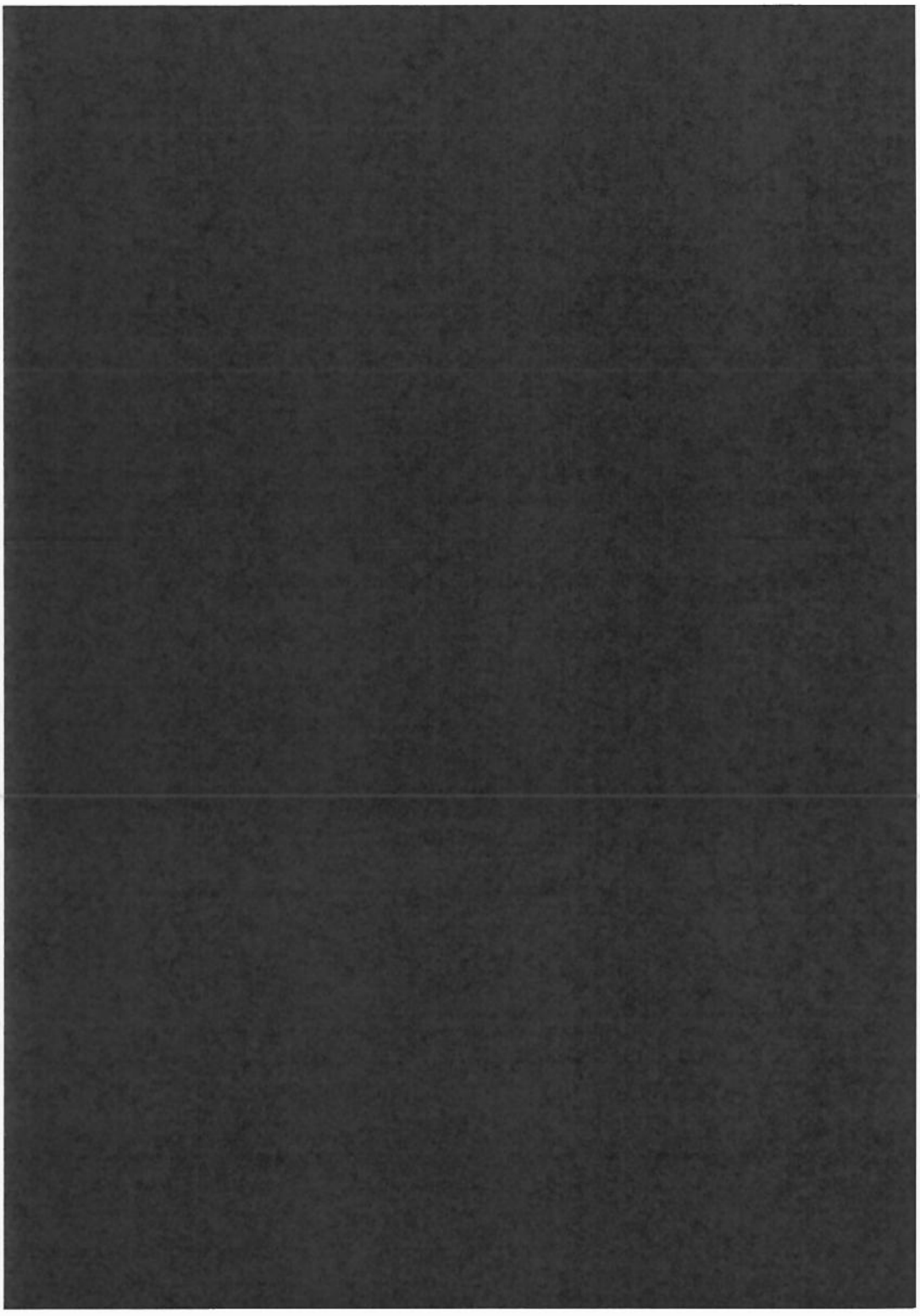

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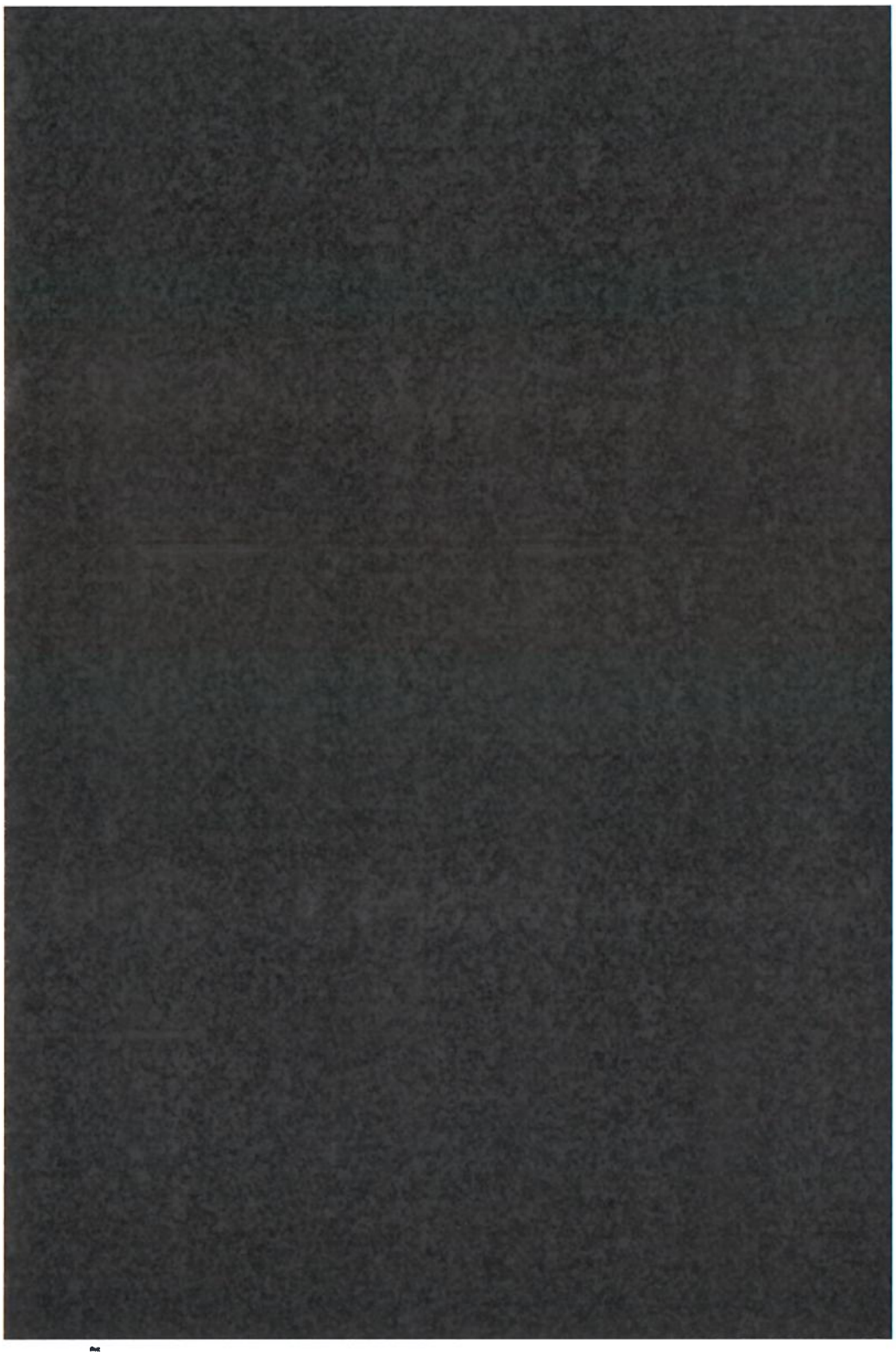

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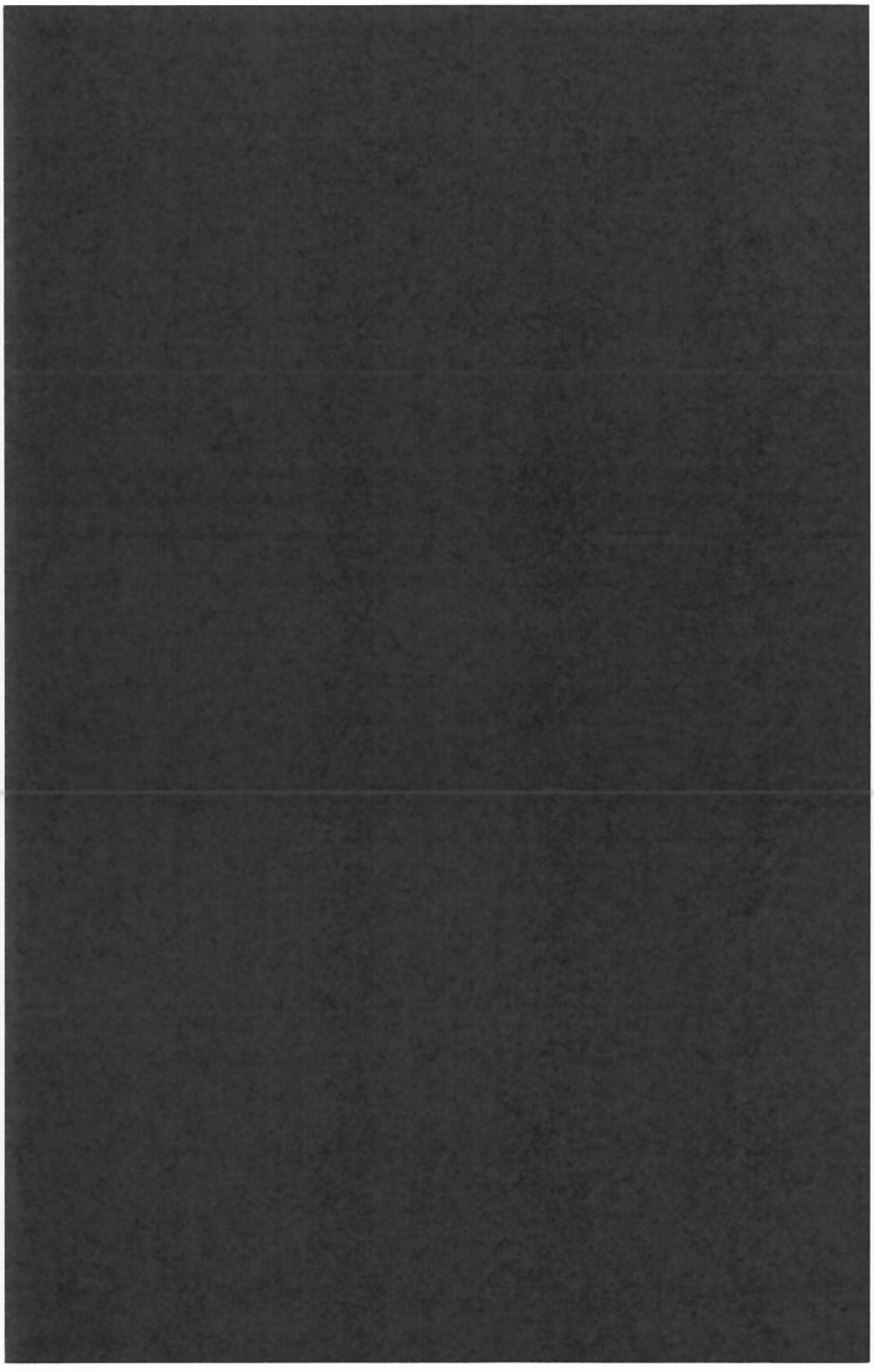

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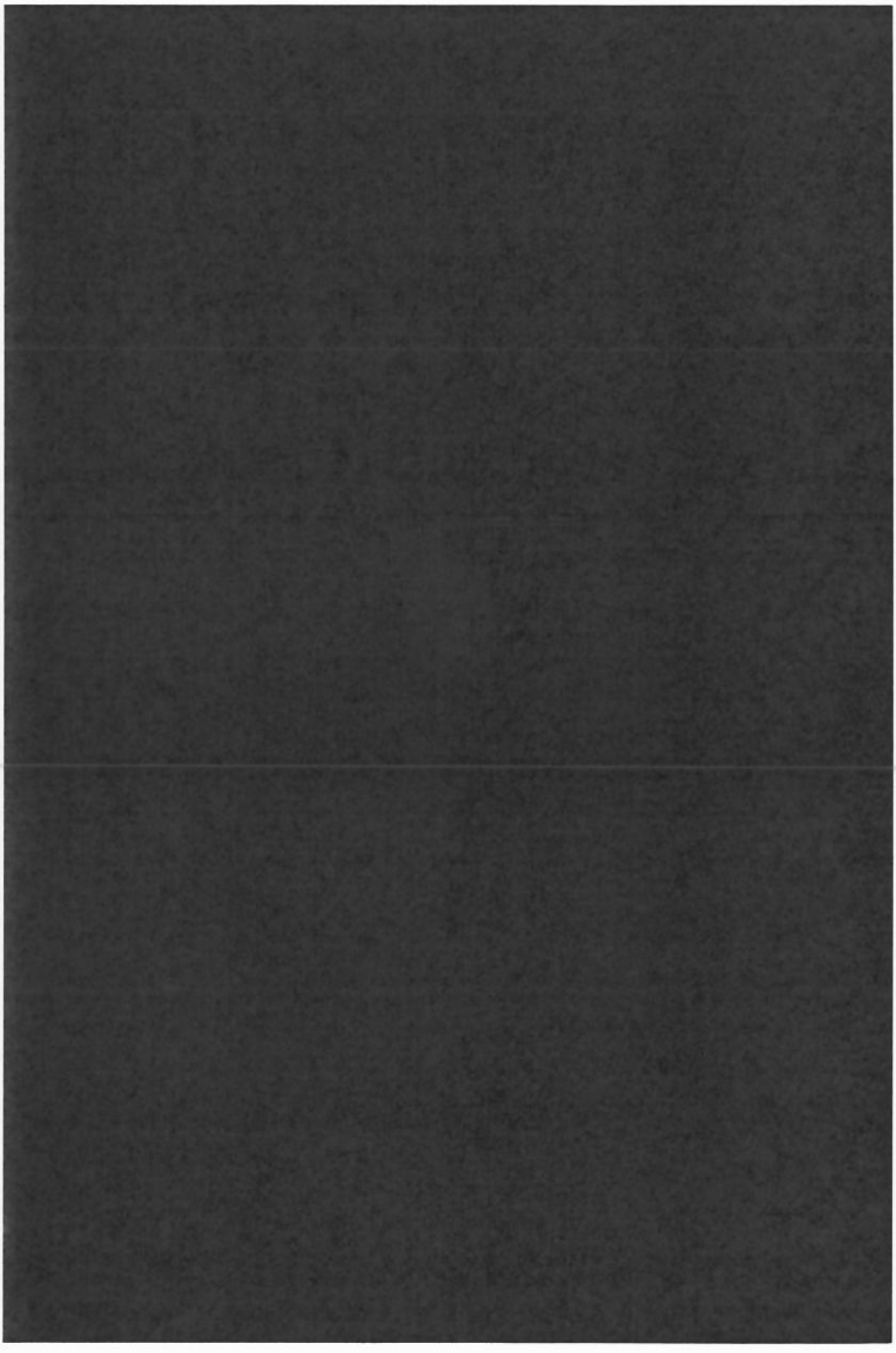

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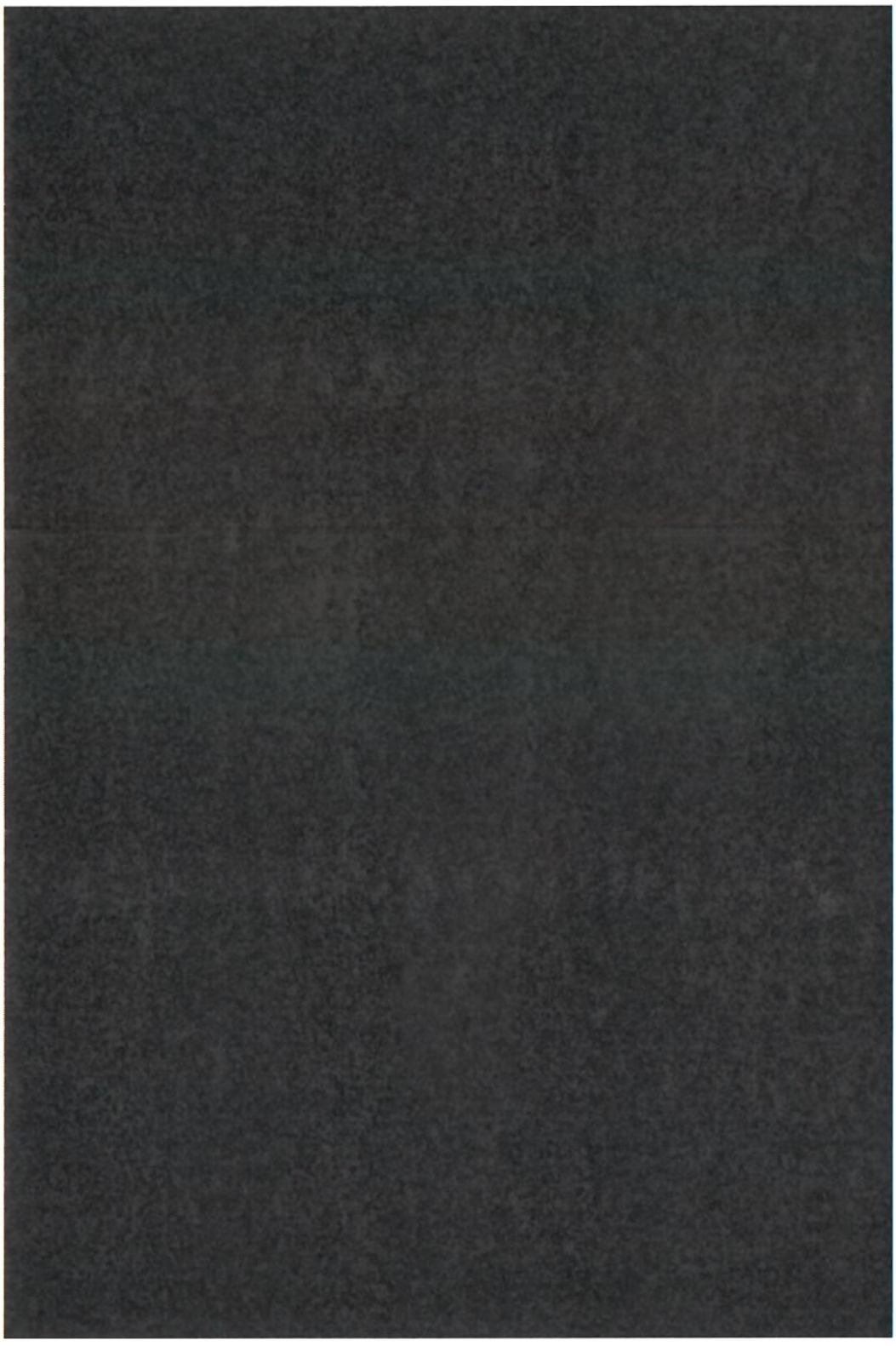

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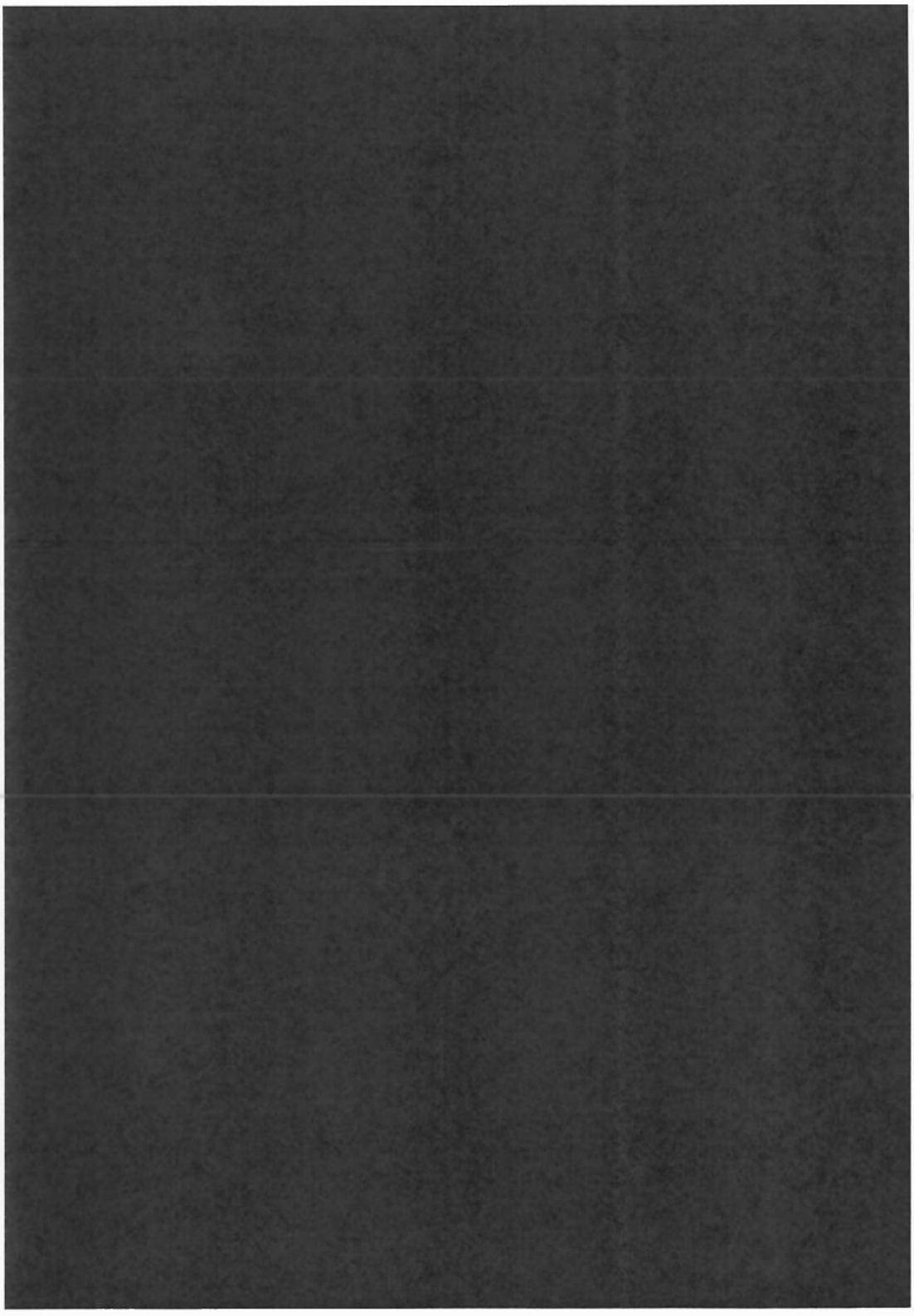

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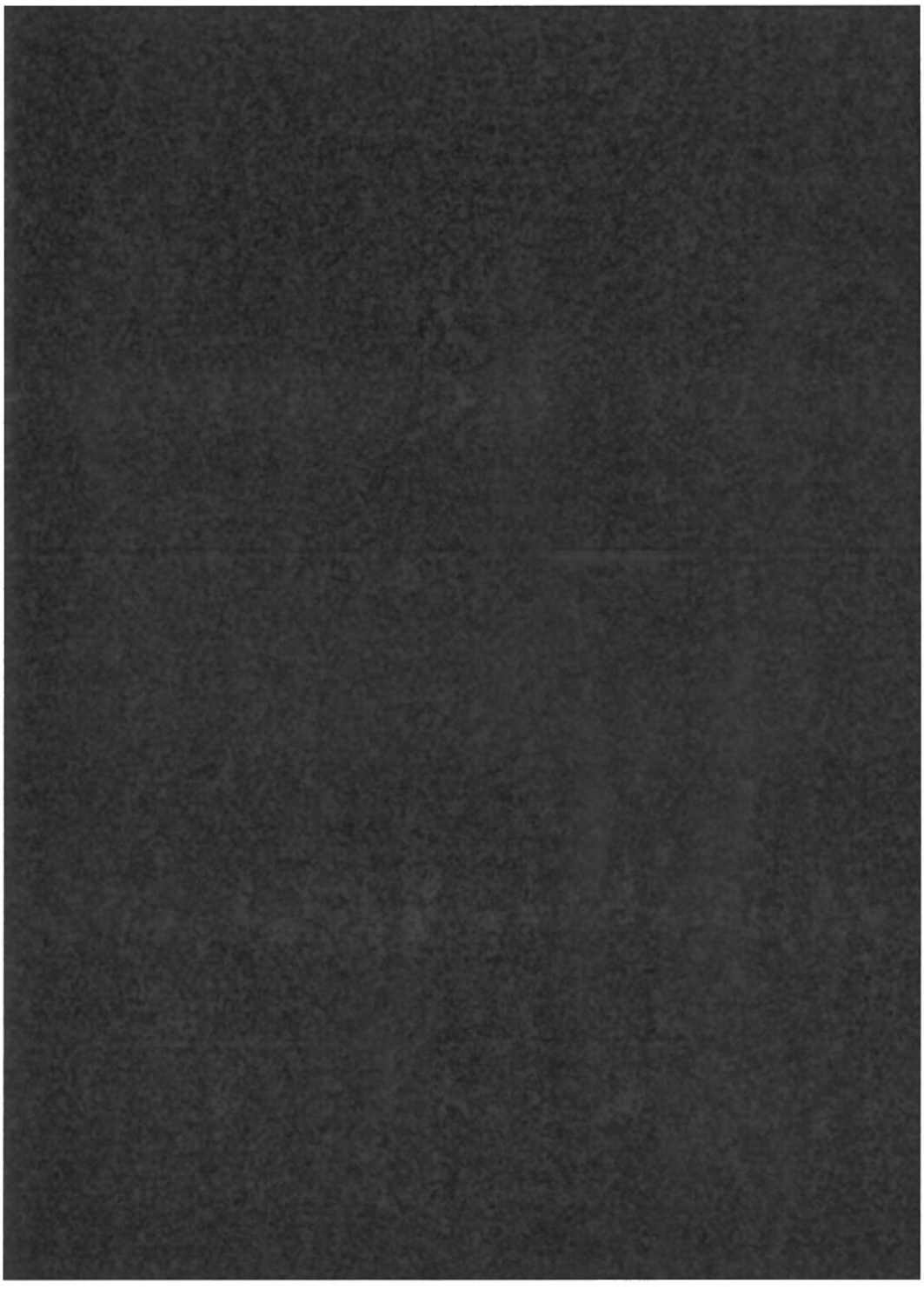

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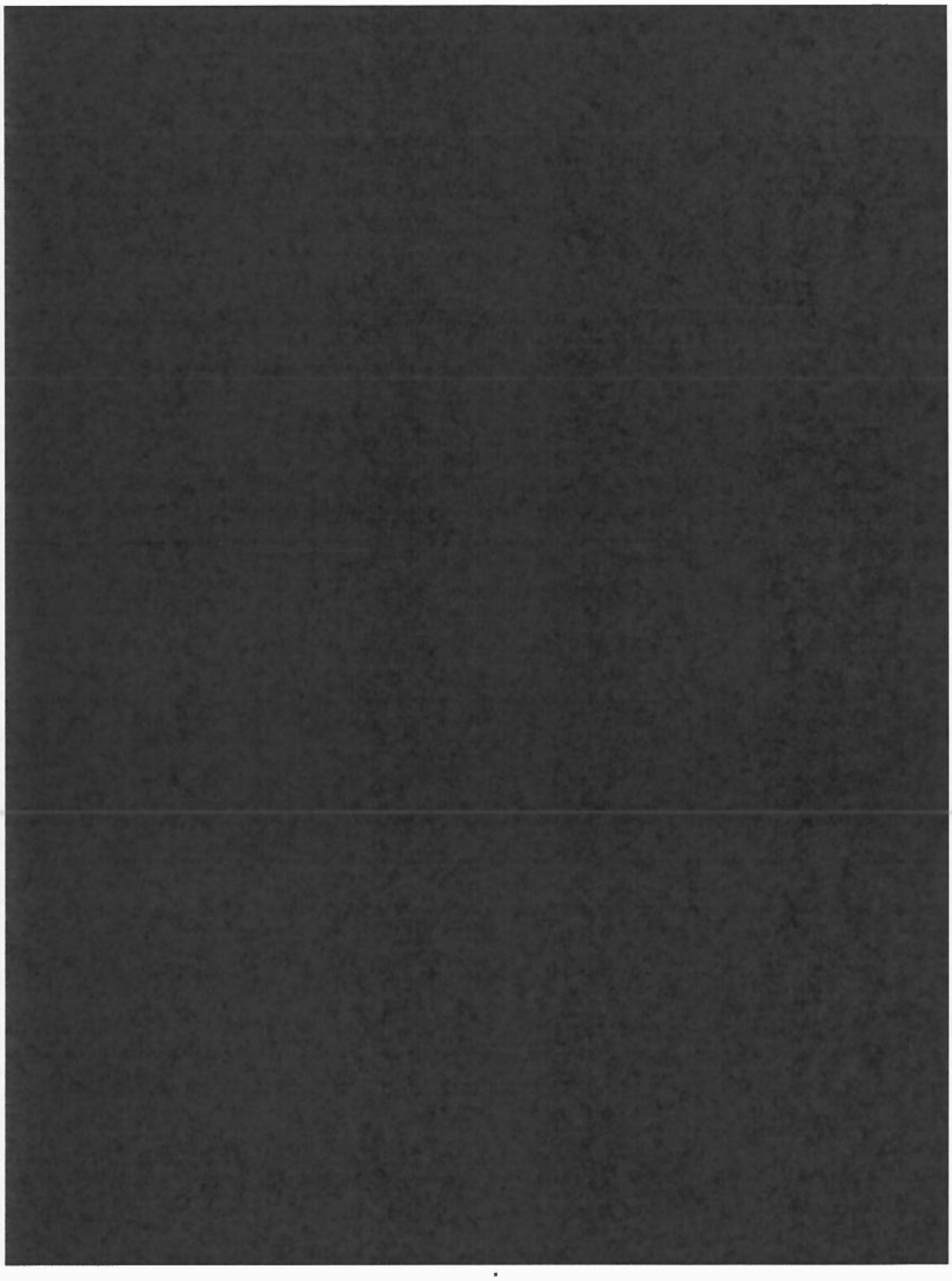

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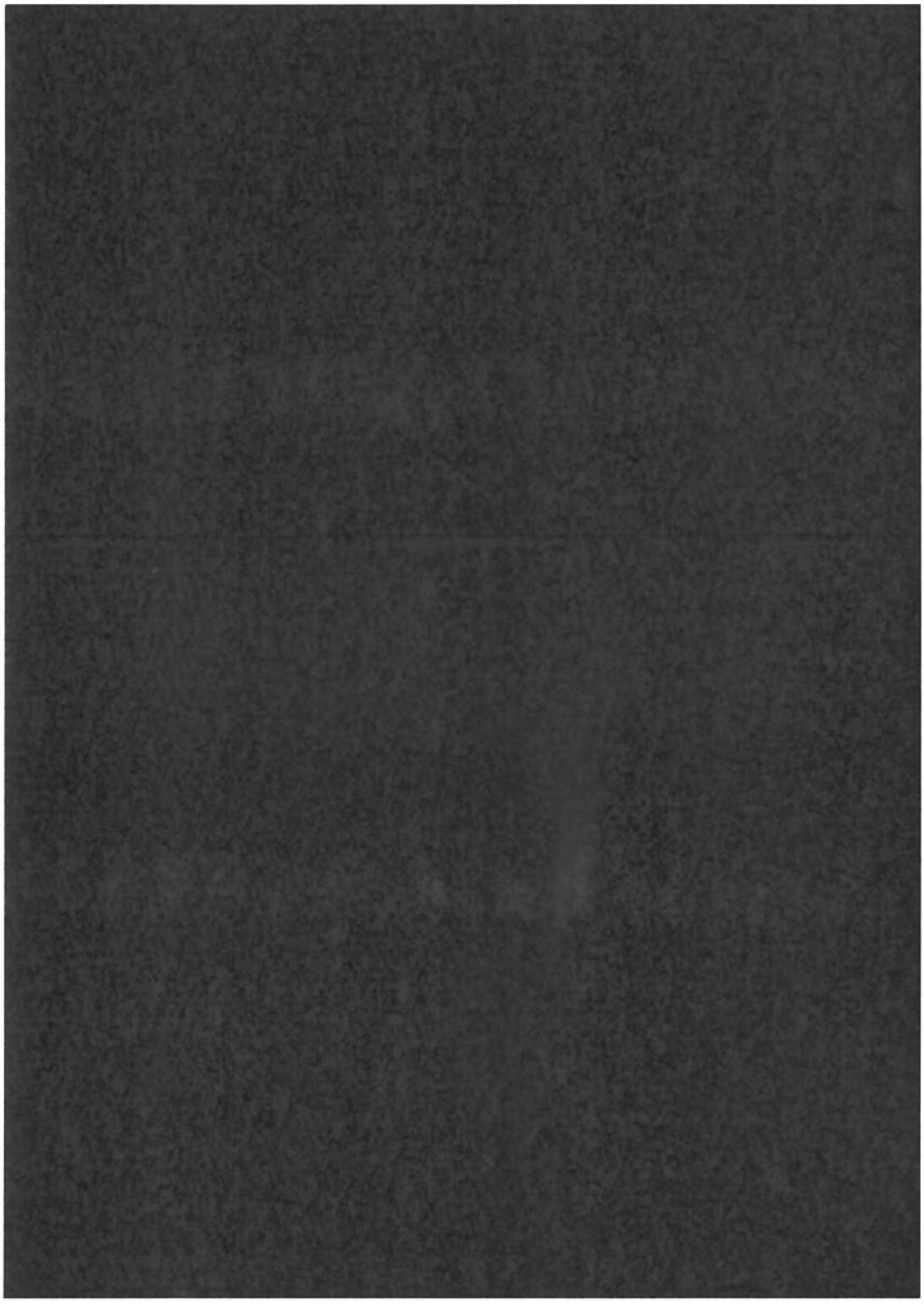

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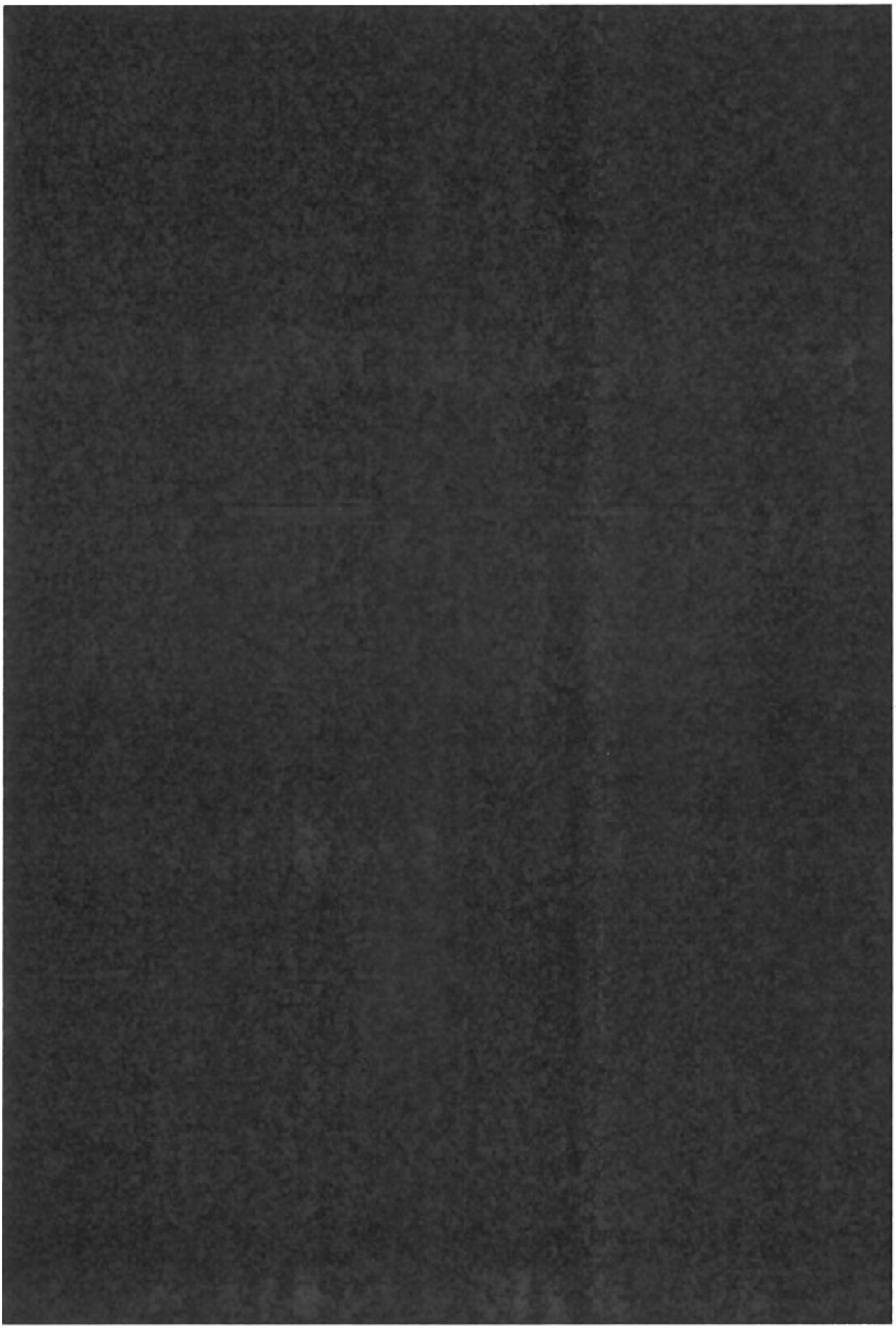

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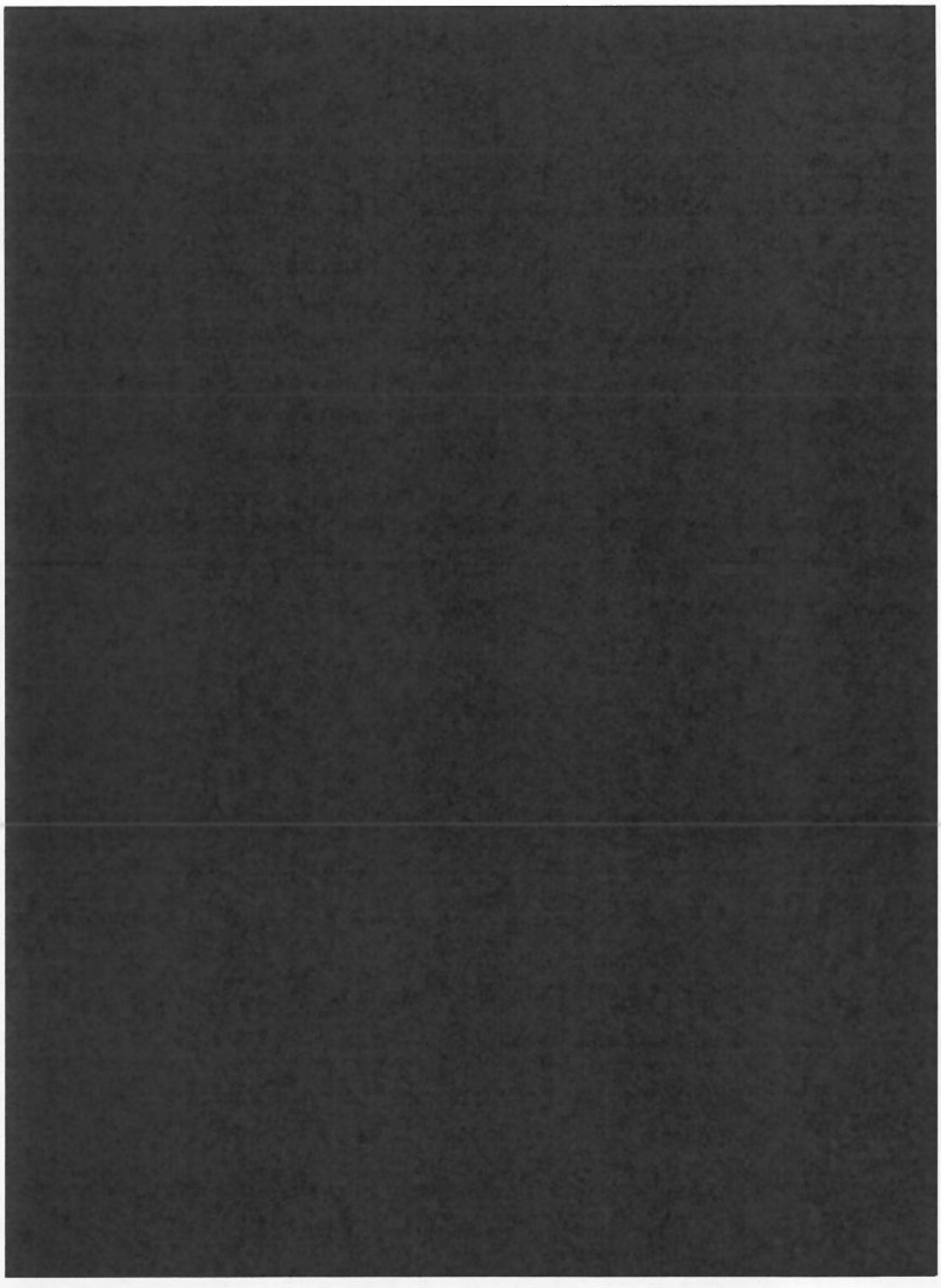

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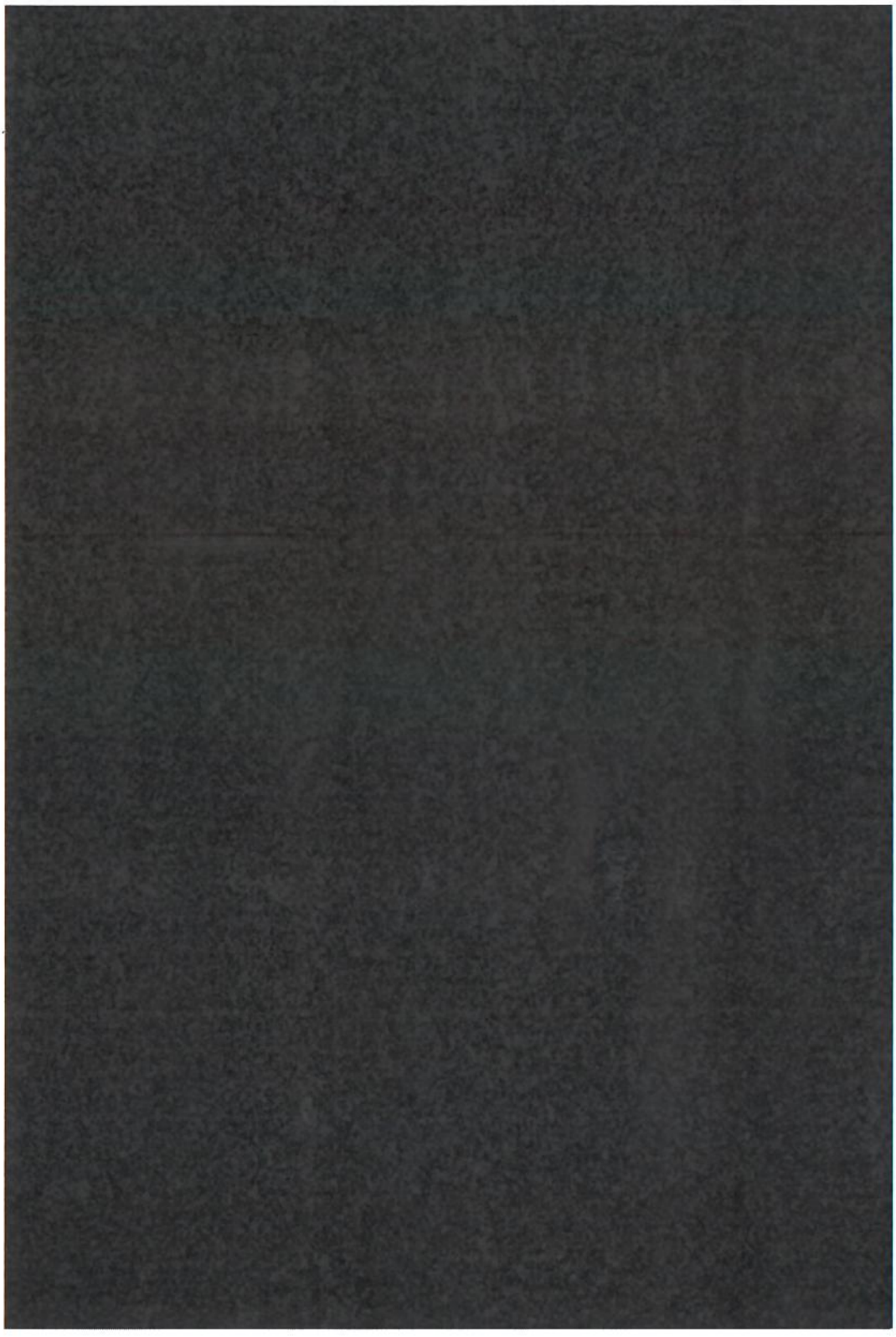

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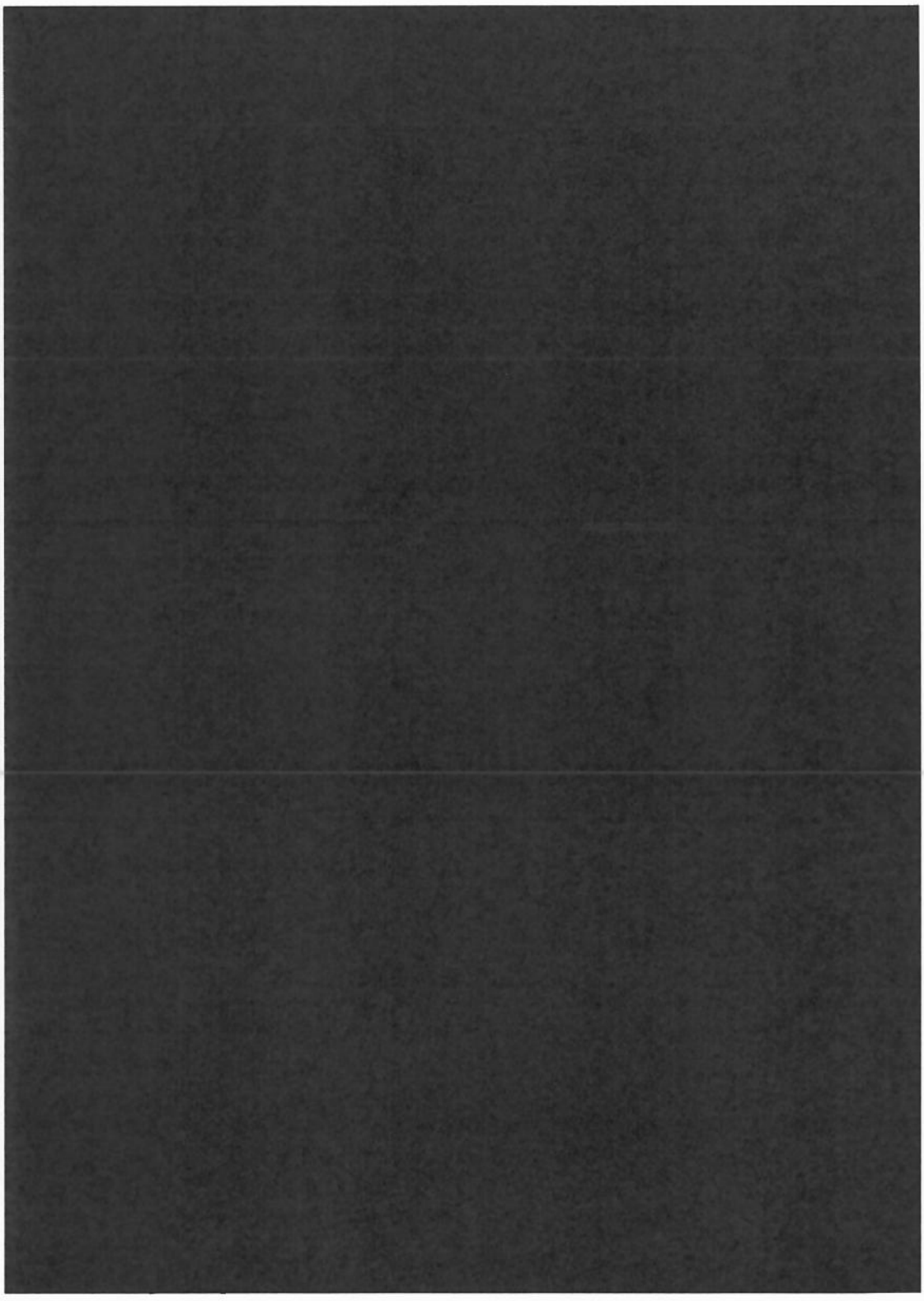

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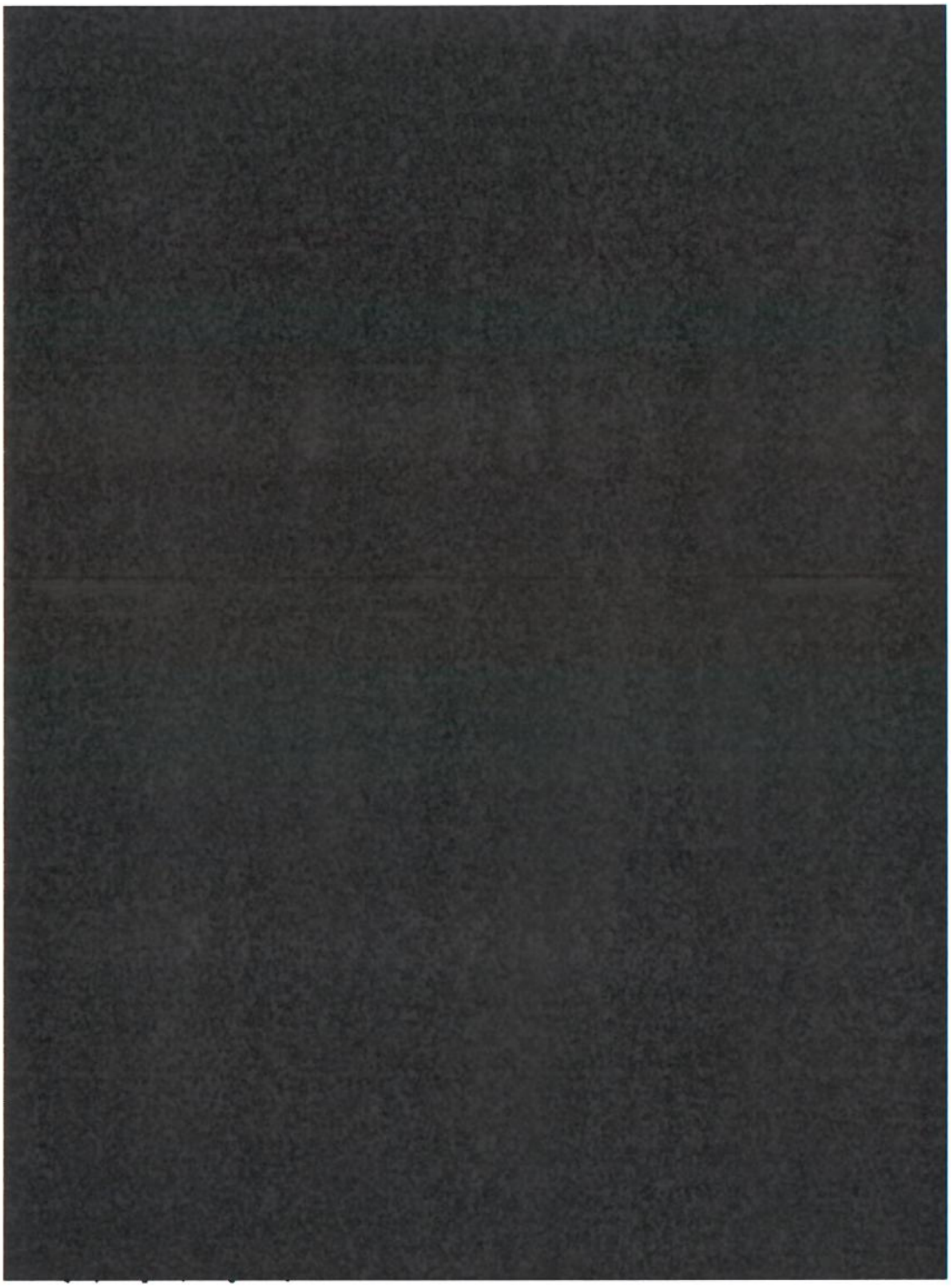

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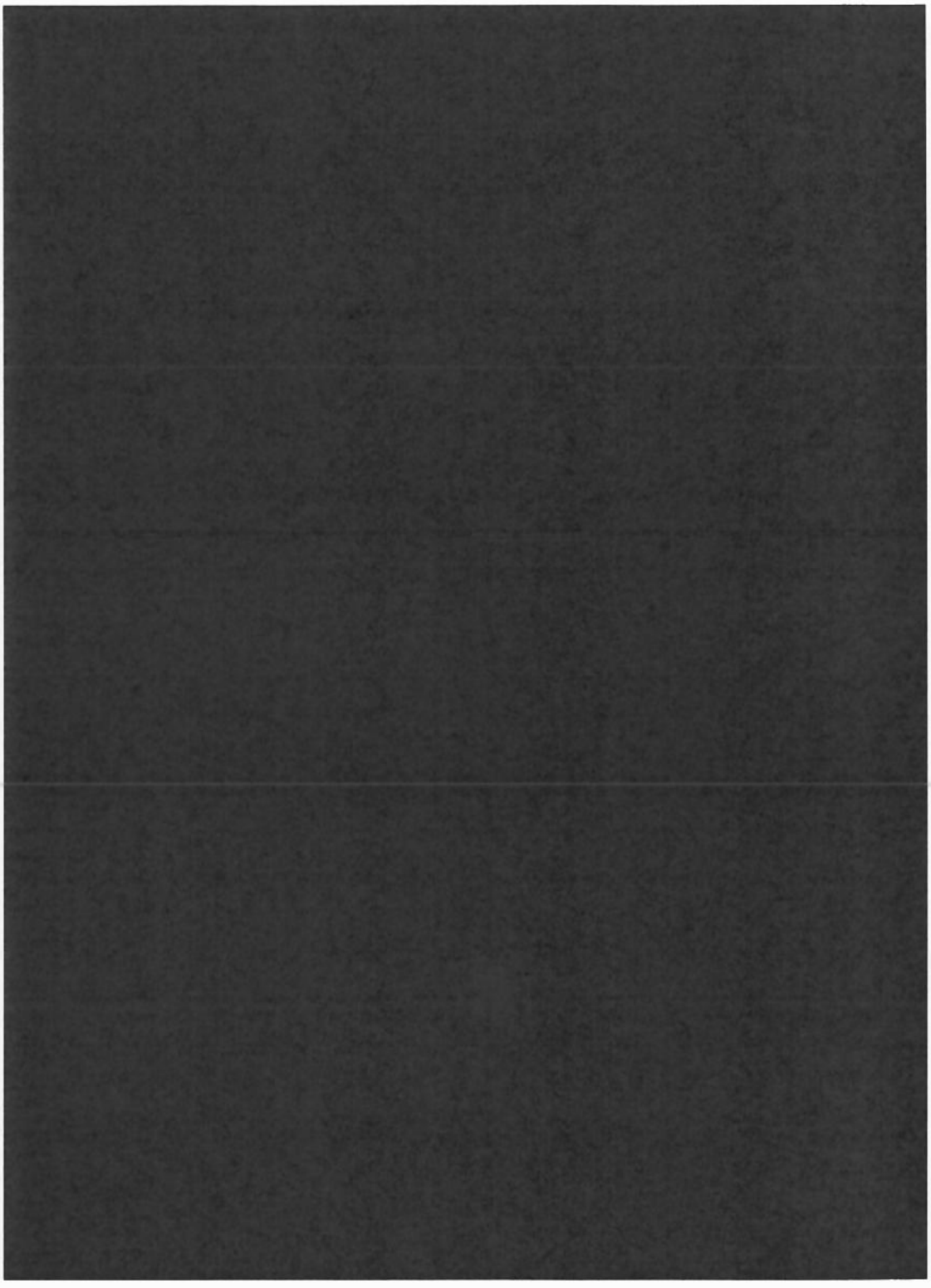

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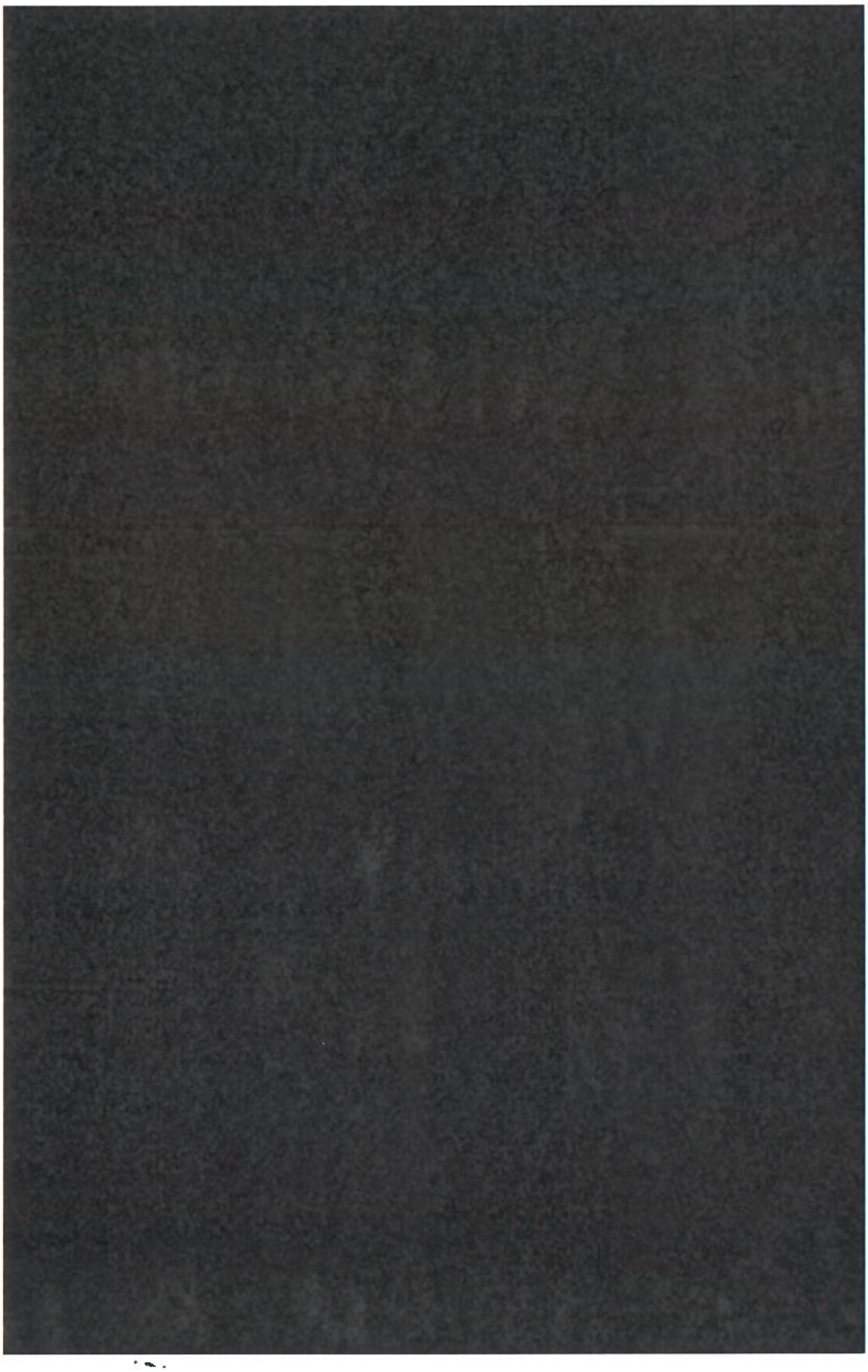

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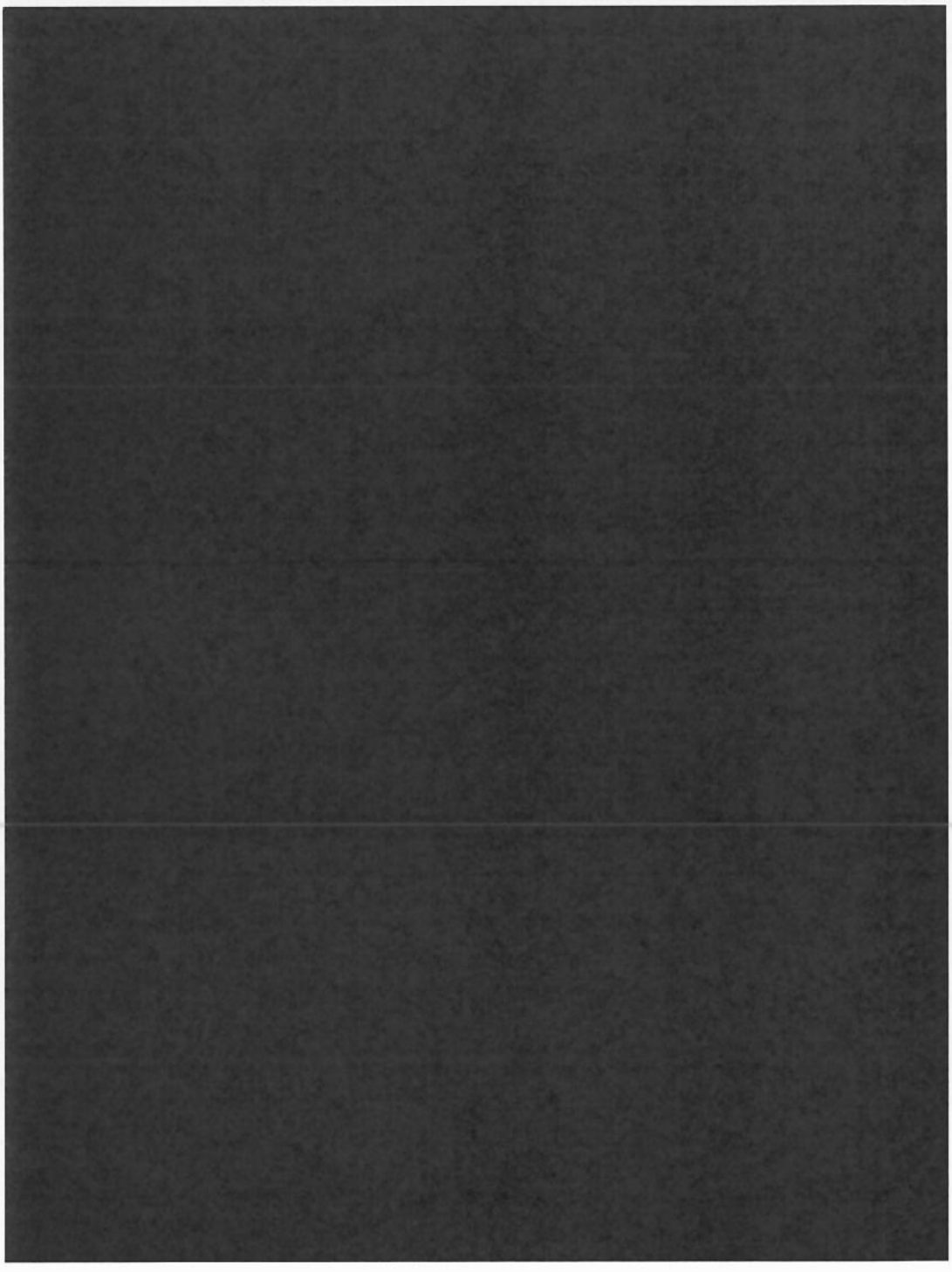

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Date December 14, 1960

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