From:	Johnson, Robert (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0851E89240324306B78740A4A60745E2-JOHNSON, RO <Robert.Johnson@hhs.gov>
To:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
CC:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	RE: Clinical Trial - BARDA lead for chloroquine/hydroxychloroquine
Date:	2020/03/25 05:50:24
Priority:	Normal
Type:	Note

Apologies for my really rude response below. I just got overwhelmed for a minute.

Please take it out of the therapeutic category.

Thanks.

Robert

Robert Johnson, Ph.D.
Director, Influenza and Emerging Infectious Diseases Division
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-401-4680
Cell: (b)(6)
email: Robert.Johnson@HHS.gov

From: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Sent: Wednesday, March 25, 2020 5:48 AM
To: Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>
Cc: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Subject: Re: Clinical Trial - BARDA lead for chloroquine/hydroxychloroquine

Robert
I am fine with it I have no issues I think is great just need to know what spend line for budget.

Sent from my iPhone

On Mar 25, 2020, at 5:21 AM, Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>wrote:

Rick and Gary,

I'm not sure what to say. This was a $750,000 award made to PPD (simplified acquisition) to so we could talk with them and work with Oacle, with whom they have experience. I mentioned on Monday's call where Rick told us about have to set up a trail in 48 hours, that we would need the CRO on immediately.

Amongst their other assets, PPD has experience with Oracle and understood how this process would work.

The award allowed us to make significant progress, without a significant commitment.

The award was made before we knew about the potential change.

Can we just get on a call to discuss if there are concerns?

Thanks.

Robert

Robert Johnson, Ph.D.
Director, Influenza and Emerging Infectious Diseases Division
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-401-4680
Cell: (b)(6)
email: Robert.Johnson@HHS.gov

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Wednesday, March 25, 2020 4:03 AM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Merkeley, Tyler (OS/ASPR/BARDA) <Tyler.Merkeley@hhs.gov>
Cc: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>; Acheampong, Otuo (OS/ASPR/BARDA) (CTR) <Otuo.Acheampong@hhs.gov>
Subject: Re: Clinical Trial - BARDA lead for chloroquine/hydroxychloroquine

I had the same question on the funding. I would like to see the plan before it is awarded. I mentioned to Robert that some of the high level strategy might be morphing and the drug supply might not materialize as Joe Hamel had hoped. Good to connect us all on a call today to align. This might end up being smaller than originally envisioned.

Great work to all. Rick

From: Gary Disbrow <Gary.Disbrow@hhs.gov>
Date: Wednesday, March 25, 2020 at 3:31 AM
To: Tyler Merkeley <Tyler.Merkeley@hhs.gov>, "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>
Cc: Gretta Blatner <Gretta.Blatner@hhs.gov>, Robert Johnson <Robert.Johnson@hhs.gov>, "Acheampong, Otuo (OS/ASPR/BARDA) (CTR)" <Otuo.Acheampong@hhs.gov>, Gary Disbrow <Gary.Disbrow@hhs.gov>
Subject: RE: Clinical Trial - BARDA lead for chloroquine/hydroxychloroquine

Team,

How was the award made to PPD? What funding was used?

Thanks

Gary

Gary L. Disbrow Ph.D.
Deputy Assistant Secretary

Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-260-0899
Mobile (b)(6)
Fax: 202-205-0873
email: Gary.Disbrow@HHS.gov

From: Merkeley, Tyler (OS/ASPR/BARDA) <Tyler.Merkeley@hhs.gov>
Sent: Tuesday, March 24, 2020 8:44 PM
To: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Cc: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>
Subject: Fwd: Clinical Trial - BARDA lead for chloroquine/hydroxychloroquine

Rick

Need an answer from you please on the below. Team is Deferring to you
We made an award to PPD today for the Expanded Access
Protocol for chloroquine/hydroxychloroquine that BARDA is running.

Are we going to want a comms package and web announcement around this effort. Before I start the process I just want to confirm since this is a unique situation. I am assuming yes but would like to confirm

Thanks

Tyler

Get Outlook for iOS

U.S. Department of Health &Human Services (HHS)

O'Neill Building
200 C Street SW
Washington, DC 20024

C [redacted] | O 202.260.0315 | F 202.205.8442 Connect on LinkedIn

MedicalCounterMeasures.gov
DRIVe.HHS.gov

Sender:	Johnson, Robert (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0851E89240324306B78740A4A60745E2-JOHNSON, RO <Robert.Johnson@hhs.gov>
Recipient:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Sent Date:	2020/03/25 05:50:23
Delivered Date:	2020/03/25 05:50:24
Message Flags:	Unread

BARDA COVID-19 Acquisitions Report - Brief Report - Active

2020-04-20 16:15:05 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Acquisition Vehicle	Obligated Amount	Date of Action	Award or Reprogramming	Project Status
(b)(4); (b)(5)							

BARDA COVID-19 Acquisitions Report - Brief Report - Pending

2020-04-20 16:15:05 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Acquisition Vehicle	Obligated Amount	Date of Action	Award or Reprogramming	Project Status
(b)(4); (b)(5)							

BARDA COVID-19 Acquisitions Report - Obligated and Active

2020-04-20 16:15:05 -04:00

Last Refreshed

(b)(4); (b)(5)

BARDA COVID-19 Acquisitions Report - Appropriation vs Obligation

2020-04-20 16:15:05 -04:00

Last Refreshed

(b)(4); (b)(5)

BARDA COVID-19 Acquisitions Report - Location Information

2020-04-20 16:15:05 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Obligated Amount	Date of Action	City	State / Province	Country

(b)(4); (b)(5)

From:	Hamel, Joseph (OS/ASPR/IO) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=96D2C1602DFA45E5A5E21452A098B96D-HAMEL, JOSE <Joseph.Hamel@hhs.gov>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Roberts, Rosemary (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4731b25305ad4907aae85267cd9e6822-rosemary.ro <Rosemary.Roberts@fda.hhs.gov>; Harrison, Brian (HHS/IOS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d145efc9c35c4865aca6e9d47786b204-Harrison, B <Brian.Harrison@hhs.gov>; Kadlec, Robert (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a182eda693d040d3832bae6efcf7a255-Kadlec, Rob <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fdeb5ca04b6b4ed19fec2209b5f571e7-Shuy, Bryan <Bryan.Shuy@hhs.gov>; Charrow, Robert (HHS/OGC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00531138af454ce3ac0b5885bead345f-Charrow, Ro <Robert.Charrow@hhs.gov>
CC:	Lenihan, Keagan (FDA/OC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3cd1b7aba9034ddb936017780583af7d-keagan.leni <Keagan.Lenihan@fda.hhs.gov>; Woodcock, Janet (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5f925e9a0f9147b186d40072d474d13d-janet.woodc <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=41bd389298db4965bf2443225fb2a4ae-patrizia.ca <Patrizia.Cavazzoni@fda.hhs.gov>; Zadecky, Leo (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=36f040c6e17d4b309f854435abb22bae-leo.zadecky <Leo.Zadecky@fda.hhs.gov>; Jensen, Valerie E (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9e00c9dcc7a64d2dabc458b5558c3823-valerie.jen <Valerie.Jensen@fda.hhs.gov>; Throckmorton, Douglas C (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=44cfe13037554ffe81729ff8f98a325c-douglas.thr <Douglas.Throckmorton@fda.hhs.gov>; Adams, Peter (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2d68d0d59aeb425cbb0ea4a46a2b9365-Adams, Pete <Peter.Adams@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>
Subject:	RE: Chloroquine
Date:	2020/03/19 14:41:28
Priority:	Normal
Type:	Note

Will do!

Strategic Innovation and Emerging Technology Manager
Assistant Secretary for Preparedness and Response
Office: 202-969-3852

Cell (b)(6)

-----Original Message-----
From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Thursday, March 19, 2020 2:31 PM
To: Roberts, Rosemary (FDA/CDER) <Rosemary.Roberts@fda.hhs.gov>; Harrison, Brian (HHS/IOS) <Brian.Harrison@hhs.gov>; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS/ASPR/IO) <Bryan.Shuy@hhs.gov>; Charrow, Robert (HHS/OGC) <Robert.Charrow@hhs.gov>
Cc: Lenihan, Keagan (FDA/OC) <Keagan.Lenihan@fda.hhs.gov>; Woodcock, Janet (FDA/CDER) <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia (FDA/CDER) <Patrizia.Cavazzoni@fda.hhs.gov>; Zadecky, Leo (FDA/CDER) <Leo.Zadecky@fda.hhs.gov>; Jensen, Valerie E (FDA/CDER) <Valerie.Jensen@fda.hhs.gov>; Throckmorton, Douglas C (FDA/CDER) <Douglas.Throckmorton@fda.hhs.gov>; Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>; Adams, Peter (OS/ASPR/BARDA) <Peter.Adams@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>
Subject: Re: Chloroquine

+ Joe Hamel and Peter Adams.

Joe, Peter, can you please add these to your market research today if you haven't already? Thanks, Rick

On 3/19/20, 2:09 PM, "Roberts, Rosemary" <Rosemary.Roberts@fda.hhs.gov> wrote:

Mr. Harrison,

Some additional information are manufacturers who are looking to return to the market (not currently on the market). BARDA may want to reach out to these companies:

- Chloroquine phosphate tablets, 150 mg and 300 mg
  - Hikma Pharmaceuticals (to be distributed by Hikma)

Jerald Andry – jandry@Hikma.com (b)(6)

- Hydroxychloroquine sulfate tablets, 200 mg
  - Hikma Pharmaceuticals (to be distributed by Hikma)

Jerald Andry – jandry@Hikma.com (b)(6)

- Mylan Pharmaceuticals (to be distributed by Mylan)

Dawn Culp – Dawn.Culp@mylan.com (b)(6)

Rosemary Roberts
2019 n-CoV FDA IMG Operations/Drug Lead
FDA/CDER/OCD

-----Original Message-----
From: Roberts, Rosemary <Rosemary.Roberts@fda.hhs.gov>
Sent: Wednesday, March 18, 2020 7:28 PM
To: Harrison, Brian (OS) <Brian.Harrison@hhs.gov>; Kadlec, Robert P (OS) <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS) <Bryan.Shuy@hhs.gov>; Charrow, Robert (OS) <Robert.Charrow@hhs.gov>; Bright, Rick (OS) <Rick.Bright@hhs.gov>

Cc: Lenihan, Keagan <Keagan.Lenihan@fda.hhs.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Zadecky, Leo <Leo.Zadecky@fda.hhs.gov>; Jensen, Valerie E <Valerie.Jensen@fda.hhs.gov>; Throckmorton, Douglas C <Douglas.Throckmorton@fda.hhs.gov>; Roberts, Rosemary <Rosemary.Roberts@fda.hhs.gov>
Subject: FW: Chloroquine

Mr. Harrison,

In response to your request:

Manufacturers with product currently available (in alphabetical order):

- Chloroquine phosphate tablets, 150 mg and 300 mg
  - Natco Pharma (distributed by Rising Pharmaceuticals)

Glenda Bryant (US Agent) glenda.bryant@syneoshealth.com (b)(6)

- Hydroxychloroquine sulfate tablets, 200 mg
  - Alkaloida Chemical Co (distributed by Sun Pharmaceutical)

Praveen Devakadaksham (US Agent)– Praveen.devakadaksham@sunpharma.com (b)(6)

- Amneal Pharmaceuticals (distributed by Amneal Pharmaceuticals)

Janie Gwinn – Janie.gwinn@amneal.com or Candis Edwards – cedwards@amneal.com (b)(6)

- Concordia Pharmaceuticals (distributed by Concordia (Plaquenil®) and Prasco Laboratories)

Wayne Vallee (US Agent) – wayne.vallee@cardinalhealth.com (b)(6)

- Sandoz (distributed by Sandoz)

Lara Hansen – lara.hansen@sandoz.com (b)(6)

- Teva Pharmaceuticals (distributed by Actavis Pharma)

Joe DeVito – Joseph.DeVito@tevapharm.com (b)(6)

- TWi Pharmaceuticals (distributed by Dr. Reddy's Laboratories)

Kumara Sekar (US Agent) – kumara.sekar@twipharmausa.com (b)(6)

- Zydus Pharmaceuticals (distributed by Northstar Rx, Zydus Pharmaceuticals)

Srinivas Gurram – Gsrinivas@zydususa.com 609-730-1900 ext. 110

Please let us know if any questions.

Rosemary Roberts
2019 n-CoV FDA IMG Operations/Drug Lead
FDA/CDER/OCD

-----Original Message-----
From: Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>
Sent: Wednesday, March 18, 2020 5:48 PM
To: Lenihan, Keagan <Keagan.Lenihan@fda.hhs.gov>; Harrison, Brian (OS) <Brian.Harrison@hhs.gov>
Cc: Kadlec, Robert P (OS) <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS) <Bryan.Shuy@hhs.gov>; Charrow, Robert (OS) <Robert.Charrow@hhs.gov>; Roberts, Rosemary <Rosemary.Roberts@fda.hhs.gov>; Throckmorton, Douglas C <Douglas.Throckmorton@fda.hhs.gov>
Subject: RE: Chloroquine

Referring to Rosemary Roberts (CDER CTECS), + Doug Throckmorton Rosemary will get manufacturer information and liaise with CDER drug shortage group.
We don't have volume data, but we can get market share.
Patrizia

-----Original Message-----
From: Lenihan, Keagan <Keagan.Lenihan@fda.hhs.gov>
Sent: Wednesday, March 18, 2020 5:44 PM
To: Harrison, Brian (OS) <Brian.Harrison@hhs.gov>
Cc: Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Kadlec, Robert P (OS) <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS) <Bryan.Shuy@hhs.gov>; Charrow, Robert (OS) <Robert.Charrow@hhs.gov>
Subject: RE: Chloroquine

HHS is trying to understand domestic supply and how we ramp that up. We need BARDAs help, but we can provide the list of domestic manufacturers for you all to call and ask them to ramp up. Not sure we have volume data, right Patrizia?

-----Original Message-----
From: Harrison, Brian (HHS/IOS) <Brian.Harrison@hhs.gov>
Sent: Wednesday, March 18, 2020 5:37 PM
To: Lenihan, Keagan <Keagan.Lenihan@fda.hhs.gov>
Cc: Cavazzoni, Patrizia <Patrizia.Cavazzoni@fda.hhs.gov>; Kadlec, Robert P (OS) <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS) <Bryan.Shuy@hhs.gov>; Lenihan, Keagan <Keagan.Lenihan@fda.hhs.gov>; Charrow, Robert (OS) <Robert.Charrow@hhs.gov>
Subject: Re: Chloroquine

+FDA

Brian Harrison
Chief of Staff
U.S. Department of Health and Human Services
202.690.7000
brian.harrison@hhs.gov

> On Mar 18, 2020, at 5:35 PM, Lenihan, Keagan <Keagan.Lenihan@fda.hhs.gov> wrote:
>
> Patrizia- connecting you with HHS leadership to help connect ASPR/BARDA with domestic manufacturers of chloroquine. We need them to ramp up production quickly.
>
> Thanks,
> Keagan
>
> Sent from my iPhone

Sender:	Hamel, Joseph (OS/ASPR/IO) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=96D2C1602DFA45E5A5E21452A098B96D-HAMEL, JOSE <Joseph.Hamel@hhs.gov>
Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Roberts, Rosemary (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=4731b25305ad4907aae85267cd9e6822-rosemary.ro

	<Rosemary.Roberts@fda.hhs.gov>; Harrison, Brian (HHS/IOS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d145efc9c35c4865aca6e9d47786b204-Harrison, B <Brian.Harrison@hhs.gov>; Kadlec, Robert (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a182eda693d040d3832bae6efcf7a255-Kadlec, Rob <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fdeb5ca04b6b4ed19fec2209b5f571e7-Shuy, Bryan <Bryan.Shuy@hhs.gov>; Charrow, Robert (HHS/OGC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00531138af454ce3ac0b5885bead345f-Charrow, Ro <Robert.Charrow@hhs.gov>; Lenihan, Keagan (FDA/OC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3cd1b7aba9034ddb936017780583af7d-keagan.leni <Keagan.Lenihan@fda.hhs.gov>; Woodcock, Janet (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=5f925e9a0f9147b186d40072d474d13d-janet.woodc <Janet.Woodcock@fda.hhs.gov>; Cavazzoni, Patrizia (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=41bd389298db4965bf2443225fb2a4ae-patrizia.ca <Patrizia.Cavazzoni@fda.hhs.gov>; Zadecky, Leo (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=36f040c6e17d4b309f854435abb22bae-leo.zadecky <Leo.Zadecky@fda.hhs.gov>; Jensen, Valerie E (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=9e00c9dcc7a64d2dabc458b5558c3823-valerie.jen <Valerie.Jensen@fda.hhs.gov>; Throckmorton, Douglas C (FDA/CDER) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=44cfe13037554ffe81729ff8f98a325c-douglas.thr <Douglas.Throckmorton@fda.hhs.gov>; Adams, Peter (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2d68d0d59aeb425cbb0ea4a46a2b9365-Adams, Pete <Peter.Adams@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>
Sent Date:	2020/03/19 14:41:27
Delivered Date:	2020/03/19 14:41:28

BARDA COVID-19 Acquisitions Report - Brief Report - Active

2020-04-17 8:34:50 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Acquisition Vehicle	Obligated Amount	Date of Action	Award or Reprogramming	Project Status

(b)(4); (b)(5)

BARDA COVID-19 Acquisitions Report - Brief Report - Pending

2020-04-17 8:34:50 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Acquisition Vehicle	Obligated Amount	Date of Action	Award or Reprogramming	Project Status
(b)(4); (b)(5)							

BARDA COVID-19 Acquisitions Report - Obligated and Active

2020-04-17 8:34:50 -04:00
Last Refreshed

(b)(4); (b)(5)

BARDA COVID-19 Acquisitions Report - Appropriation vs Obligation

2020-04-17 8:34:50 -04:00
Last Refreshed

(b)(4); (b)(5)

BARDA COVID-19 Acquisitions Report - Location Information

2020-04-17 8:34:50 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Obligated Amount	Date of Action	City	State / Province	Country
(b)(4); (b)(5)							

From:	Lambert, Linda (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CE6824B6A92A4A4E893EA7B54E17EB3C-LAMBERT, LI <Linda.Lambert@hhs.gov>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>
Subject:	NIAID offered up Libby Higgs. EUA access plan for CQ and HCQ
Date:	2020/03/26 15:53:11
Priority:	Normal
Type:	Note

From: Lambert, Linda (OS/ASPR/BARDA)
Sent: Thursday, March 26, 2020 3:52 PM
To: Marston, Hilary (NIH/NIAID) [E] <hilary.marston@nih.gov>
Cc: Beigel, John (NIH) [E] <jbeigel@niaid.nih.gov>; Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Higgs, Elizabeth (NIH/NIAID) [E] <ehiggs@niaid.nih.gov>
Subject: RE: Please join - call going now re EUA access plan for CQ and HCQ

Thank you Hilary, thank you Libby, and thank you NIAID.

From: Marston, Hilary (NIH/NIAID) [E] <hilary.marston@nih.gov>
Sent: Thursday, March 26, 2020 3:50 PM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Beigel, John (NIH) [E] <jbeigel@niaid.nih.gov>; Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Higgs, Elizabeth (NIH/NIAID) [E] <ehiggs@niaid.nih.gov>
Subject: Re: Please join - call going now re EUA access plan for CQ and HCQ

Understood Linda and appreciated. Libby Higgs has been immersed in the data and would be able to offer this input.

From: Linda Lambert <Linda.Lambert@hhs.gov>
Date: Thursday, March 26, 2020 at 2:44 PM
To: Hilary Marston <hilary.marston@nih.gov>
Cc: John Beigel <jbeigel@niaid.nih.gov>, "Walker, Robert (OS/ASPR/BARDA)" <Robert.Walker@hhs.gov>
Subject: RE: Please join - call going now re EUA access plan for CQ and HCQ

Sorry that there was a scheduling conflict Hilary.
We need and highly value NIAID's engagement and expertise in providing clinical perspectives as part of the interagency.
Will that work?

Linda

From: Marston, Hilary (NIH/NIAID) [E] <hilary.marston@nih.gov>
Sent: Thursday, March 26, 2020 2:37 PM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Beigel, John (NIH) [E] <jbeigel@niaid.nih.gov>; Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>
Subject: Re: Please join - call going now re EUA access plan for CQ and HCQ

Sorry we are both on the vax wg call. Still, NIH doesn't really have a role in the eua?

On Mar 26, 2020, at 2:35 PM, Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>wrote:

Dear John and Hilary
Bob Walker sent out a meeting invite for the clinical call. He moves fast!
It's important to have your input as part of our interagency partnership.
Can you dial in or identify someone quickly who can participate?
Linda

Sender:	Lambert, Linda (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CE6824B6A92A4A4E893EA7B54E17EB3C-LAMBERT, LI <Linda.Lambert@hhs.gov>
Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>
Sent Date:	2020/03/26 15:53:10
Delivered Date:	2020/03/26 15:53:11

From:	Hamel, Joseph (OS/ASPR/IO) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=96D2C1602DFA45E5A5E21452A098B96D-HAMEL, JOSE <Joseph.Hamel@hhs.gov>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
CC:	Shuy, Bryan (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fdeb5ca04b6b4ed19fec2209b5f571e7-Shuy, Bryan <Bryan.Shuy@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
Subject:	RE: HCQ donation
Date:	2020/03/23 15:07:56
Priority:	Normal
Type:	Note

Was typing as I got this... Connection inbound..

Strategic Innovation and Emerging Technology Manager
Assistant Secretary for Preparedness and Response
Office: 202-969-3852
Cell: (b)(6)

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Monday, March 23, 2020 3:02 PM
To: Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>
Cc: Shuy, Bryan (OS/ASPR/IO) <Bryan.Shuy@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Subject: HCQ donation

Joe,

We really need your help. Would you mind maintaining your connection with Sandoz/Novartis and coordinate a supply of CQ and HCQ donation to be directed to the NIH PCORI trial that is trying to standup today? I can connect you with NIH and I think you have the Sandoz connection. Charrow said this would not interfere with their process.

I really need your help to make this happen as soon as possible today. Can you please help make the connections and watch the magic happen?

Thanks Rick

Sender:	Hamel, Joseph (OS/ASPR/IO) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=96D2C1602DFA45E5A5E21452A098B96D-HAMEL, JOSE <Joseph.Hamel@hhs.gov>
Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Shuy, Bryan (OS/ASPR/IO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=fdeb5ca04b6b4ed19fec2209b5f571e7-Shuy, Bryan <Bryan.Shuy@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
Sent Date:	2020/03/23 15:07:55
Delivered Date:	2020/03/23 15:07:56

From:	Martin VanTrieste <martin@civicarx.org>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	Heads-Up
Date:	2020/03/26 10:47:41
Priority:	Normal
Type:	Note

Civica's supplier of hydroxychloroquine was located in Hungary. The Hungarian authorities, I suspended the export of essential medications. There are several API and finished product manufacturers located in Hungary...

Martin VanTrieste | President and CEO
Serving Patients is Our Privilege

2912 Executive Parkway, Ste. 325
Lehi, UT 84043
mobile (b)(6)
email |martin@civicarx.org
web | https://protect2.fireeye.com/url?k=dfe40446-83b01d3a-dfe43579-0cc47adc5fa2-1c5424871731d03b&u=http://www.civicarx.org/

Sender:	Martin VanTrieste <martin@civicarx.org>
Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Sent Date:	2020/03/26 10:45:28
Delivered Date:	2020/03/26 10:47:41

SNS Hydroxychloroquine/Chloroquine Requests

Requestor/State	Clinical Trial Material	Hydroxychloroquine/ Chloroquine	# of Pills*	Date
South Dakota Department of Health		Hydroxychloroquine	187,200	Received 04/11/20
Department of Veteran's Affairs		Hydroxychloroquine	1,008,000	Received 04/09/20
Henry Ford Hsopital,2799 West Grand Blvd, A-Basement Pharmacy, Detroit, MI		Hydroxychloroquine	100,800	Received 04/09/20
NRDC McKesson Warehouse 8313 Polk Lane, Olive Branch, MS 38654		Hydroxychloroquine	4,003,200	Received 04/09/20
AmerisourceBergen, 6305 La Salle Drive, Lockbourne, OH 43137		Hydroxychloroquine	1,003,200	Received 04/09/20
AmerisourceBergen, 6001 Global Distribution Way, Louisville, KY 40228		Hydroxychloroquine	4,003,200	Received 04/09/20
Federal Bureau of Prisons, 1000 Air Base Rd, Pollock, LA 71467		Hydroxychloroquine	120,000	Received 04/10/20
Cardinal Health Wheeling, WV 26003		Hydroxychloroquine	345,600	Received 04/09/20
Cardinal Health Lakeland, Fl 33805		Hydroxychloroquine	196,800	Received 04/10/20
Cardinal Health St. Charles, Mo 63301		Hydroxychloroquine	196,800	Received 04/10/20
Cardinal Health Staford, TX 77477		Hydroxychloroquine	196,800	Received 04/10/20

*Calculations of pills and bottles/blister packs are made by RQA based on data provided by SNS for cases of product. These amounts are based on assumptions and may not be exact.

HCQ (100 pills/bottle): 35,918 Bottles* Remain (4/16/20 donation from Mylan)
CQ (250 pills/pack): 3,952 Blister Packs* Remain

FOUO

SNS Hydroxychloroquine/Chloroquine Requests

Requestor/State	Clinical Trial Material	Hydroxychloroquine/ Chloroquine	# of Pills*	Date
Cardinal Health Groveport, OH 43125		Hydroxychloroquine	3,048,000	Received 04/09/20
Cardinal Health		Hydroxychloroquine	3,081,600	Received on 04/07/2020
Amerisource		Hydroxychloroquine	3,216,000	Received on 04/07/2020
McKesson		Hydroxychloroquine	3,024,000	Received on 04/07/2020
Seminole Tribe of Florida		Hydroxychloroquine	9600	Received on 04/07/2020
North Carolina Division of Public Health		Hydroxychloroquine	998,400	Received 04/05/2020(993,600) Received 04/06/2020(4800)
Nevada Public Health & Human Services		Hydroxychloroquine	14,400	Received 04/06/2020
Mississippi Dept of Public Health		Hydroxychloroquine	24,000	Received 04/05/2020(14,400) Received 04/07/2020(9600)
California Dept of Public Health		Hydroxychloroquine	3,297,400	Received 04/06/2020
Henry Ford Hospital, Detriot MI	Yes	Hydroxychloroquine	81,600	Received 4/05/2020
US Virgin Islands		Hydroxychloroquine	19,200	Received 04/03/2020
California, LA County Public Health		Hydroxychloroquine	28,800	Received 04/03/2020
New York, NYS Dept of Corrections and Community Supervision Central Pharmacy		Hydroxychloroquine	139,200	Received 04/03/2020

FOUO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the Assistant Secretary for
Preparedness & Response
Biomedical Advanced Research &
Development Authority (BARDA)
Washington, D.C. 20201

March 27, 2020

Stephen M. Hahn, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Re: Request for Emergency Use Authorization
Use of chloroquine phosphate or hydroxychloroquine sulfate for Treatment of COVID-19

Dear Dr. Hahn,

The Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response (ASPR), is submitting this request for Emergency Use Authorization (EUA) for the following drugs to be distributed from the Strategic National Stockpile (SNS) to public health authorities for treatment of COVID-19 during the current public health emergency:

- chloroquine phosphate
- hydroxychloroquine sulfate

BARDA also refers to the Food and Drug Administration (FDA) final guidance entitled, *"Emergency Use Authorization of Medical Products and Related Authorities"* (January 2017).

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19. Pursuant to Section 564 of the Act, and on the basis of such determination, the Secretary of HHS then declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the Act, subject to terms of any authorization issued under that section. The Secretary has also issued a Declaration pursuant to section 319F-3 of the Public Health Service Act (42 U.S.C. 247d-6d) to provide liability immunity for activities related to medical countermeasures against COVID-19.

Chloroquine phosphate and hydroxychloroquine sulfate are not FDA-approved for treatment of COVID-19. Some versions of chloroquine phosphate are approved by FDA for other indications—for suppressive treatment and acute attacks of certain strains of malaria and for the treatment of extraintestinal amebiasis, but the chloroquine phosphate drug product to be covered by this EUA has not been FDA-approved. Several versions of hydroxychloroquine sulfate are approved by FDA for prophylaxis of and treatment of malaria, treatment of lupus erythematosus, and treatment of rheumatoid arthritis.

Based upon limited in-vitro and anecdotal data, chloroquine phosphate and hydroxychloroquine sulfate are currently recommended for treatment of hospitalized COVID-19 patients in several countries, and a number of national guidelines report incorporating recommendations regarding use of chloroquine phosphate or hydroxychloroquine sulfate in the setting of COVID-19.

This EUA request is for the following uses of chloroquine phosphate and hydroxychloroquine sulfate; product will be distributed by the Strategic National Stockpile:

chloroquine phosphate
250 mg tablets supplied in blister packs containing ten 250 mg tablets that is not approved by FDA for any indication.

Administered by a healthcare provider under a valid prescription to treat the following populations:

- Adults and adolescent patients who weigh 50 kg or more and are hospitalized for COVID-19 infection;
- Patients for whom participation in a clinical trial is not available or feasible.

hydroxychloroquine sulfate
200 mg tablet that is approved by FDA for other uses and accompanied by its FDA-approved labeling and authorized Fact Sheets.

Administered by a healthcare provider under a valid prescription to treat the following populations:

-
- Adult and adolescent patients who weigh 50 kg or more and are hospitalized for COVID-19 infection;
- Patients for whom participation in a clinical trial is not available or feasible.

The request for emergency use of chloroquine and hydroxychloroquine is based on collaborative, USG-interagency effort to rapidly respond to this continuously evolving public health emergency. The breadth and scope of the intended uses of chloroquine or hydroxychloroquine in this public health emergency will continue to be assessed by clinical experts from FDA, BARDA, and Centers for Disease and Control Prevention.

On behalf of the USG interagency group responding to COVID-19, we appreciate FDA leading this effort to combat COVID-19.

If you have any questions or comments regarding this submission, please contact Tremel Faison, Director (acting) of Regulatory and Quality Affairs at Tremel.Faison@hhs.gov or at 301-956-3096.

Sincerely,

Rick Bright, Ph.D.
Director
Biomedical Advanced Research and Development Authority (BARDA)
Office of Assistant Secretary for Preparedness and Response (ASPR)
U.S. Department of Health and Human Services (HHS)

From:	Hamel, Joseph (OS/ASPR/IO) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=96D2C1602DFA45E5A5E21452A098B96D-HAMEL, JOSE <Joseph.Hamel@hhs.gov>
To:	Lenihan, Keagan (FDA/OC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=3cd1b7aba9034ddb936017780583af7d-keagan.leni <Keagan.Lenihan@fda.hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	RE: Hydroxychloroquine supply (>100 million tablets) + other COVID-19 therapeutic updates
Date:	2020/03/19 13:48:23
Priority:	Normal
Type:	Note

Fantastic – Thank you Keagan!

Strategic Innovation and Emerging Technology Manager
Assistant Secretary for Preparedness and Response
Office: 202-969-3852
Cell: (b)(6)

From: Lenihan, Keagan <Keagan.Lenihan@fda.hhs.gov>
Sent: Thursday, March 19, 2020 1:47 PM
To: Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Subject: Fwd: Hydroxychloroquine supply (>100 million tablets) + other COVID-19 therapeutic updates

Looks like Mylan might be a good bet. Can we check with them about this? 50 million for off label use would be very helpful!

Sent from my iPhone

Begin forwarded message:

From: "Hahn, Stephen" <SH1@fda.hhs.gov>
Date: March 19, 2020 at 1:41:14 PM EDT
To: "Lenihan, Keagan" <Keagan.Lenihan@fda.hhs.gov>, "Shah, Anand" <Anand.Shah@fda.hhs.gov>, "Amin, Stacy" <Stacy.Amin@fda.hhs.gov>, "Rom, Colin" <Colin.Rom@fda.hhs.gov>
Subject: Fwd: Hydroxychloroquine supply (>100 million tablets) + other COVID-19 therapeutic updates

As per our conversation

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HHS COVID-19 Top Highlights

April 9, 2020

Top Updates

- The Data Analytics team completed an updated model of the vent requirements under current mitigation measures that forecasted a maximum requirement of 50k vents at the peak of the response. There are currently over 70k vents in hospital inventories across the nation, with approximately 26k in use today.
    - The ability to move vents will need to be strategically managed as a federal asset.
    - All states are now reporting their data to HHS/FEM for use in daily ventilator usage report.
- Ventilators from the SNS were shipped to CO (100), MA (100) and Navajo Area IHS (50) to full critical needs
- Region 1 is rerouting 2 (250-bed) FMS that were sent to MA and sending them to CT and RI. One will be set up at Webster Bank Arena (Bridgeport, CT) and the other will be set up at Lowes Building (North Kingston, RI)
- CT: First responder agencies are requesting priority testing for staff as they are losing staff while awaiting test results
- 25,209 (-828) - Total Hospital Projected Bed Capacity
    - (USACE) – 17 (+0) Alternate Care Sites (ACS) = 14,759 (-828) total projected bed capacity

What Have We Done

- Community Based Testing:
    - 41 total sites: 26 live, 1 in progress, 4 closed, and 11 transitioned to state management
        - Overall: 81,034 people have been screened and 73,433 have been tested since March 23
        - Tests Processed: 61,919 tests processed; 12,593 positive results, 538 indeterminate results

- CDC published two Morbidity and Mortality Weekly Report (MMWR) Early Release articles:
    - Community Transmission of SARS-CoV-2 at Two Family Gatherings — Chicago, Illinois, February–March 2020.
    - Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020.

- New procurements/donations
    - 10M doses of Hydroxychloroquine donated by Mylan approved with 1.5-2M tabs per week; administered per FDA/BARDA EUA
    - $17.2M contract awarded to Rite Aid for COVID-19 Self-Swab and Point-of-Care Testing services
    - NTE $2M contract awarded to Estes Express for COVID-19 transportation services
    - $1.2M contract awarded to Ferno Military Systems for 300 headwall systems for High Acuity Kits
    - Modified contract with Asia Pacific for an additional $2.8M for COVID-19 transportation services

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- SNS Procurements
  - NTE $8.5M authorization to proceed with purchase of FMS Kitting Products and shipping from South Company Supply was issued. Vendor will provide product for 100 kits to complete the kitting and build of 250 bed FMS sets.
  - NTE $22.7M authorization to proceed with purchase of FMS Kitting Product Replacement and shipping from Medline Industries was issued for building 250 bed FMS sets.
- (b)(4) ventilators immediately available remaining SNS, and (b)(from DoD at Joint Base in (b)(awaiting allocation.

PPE

- Nearly, 3,000 donations and offers of support have been processed through the NBEOC Service Desk
- DoD provided 10.5 Million N95s to FEMA/HHS for distribution; 8.5 Million of these have been distributed to 7 cities (and are captured in the above table in Donations). The remaining N95s will be distributed to future areas of need by medical distributors
- The totals from April 7 to April 8 have decreased due to several procurements showing as cancelled in LCSMS.

ALL PPE DONATIONS, PROCUREMENTS, and SNS SHIPMENTS (as of 6:15 p.m. April 8)

Source	B. N95s	C. Surgical Masks	D. Gloves	E. Surgical Gowns	Total
Donation	14,468,920	2,650,000	680,570	254,852	**18,054,342**
Procured	11,763,068	1,602,750	6,279,392	34,243	**19,879,473**
SNS	11,706,103	26,533,462	22,240,997	4,357,481	**64,838,043**
Total	**37,938,111**	**30,986,212**	**29,200,959**	**4,646,576**	**102,771,858**

TASK FORCES

- CBTS TF: 11 community based testing sites have fully transitioned to state management;; positive commentary in the media on CBT sites; some sites will soon be able to utilize nasopharyngeal (NA) swabs. Just in time media shipment began to arrive at each site on April 8, follow-on will arrive next week

- Community Mitigation TF: Developing plan for indicators and thresholds that will inform communities on when they can safely reopen the community and allow people to return to work; Risk Team looking at strategies and outreach possibilities to address the higher rates of complications and deaths among African-American COVID-19 patients compared to other races/ethnic groups

- Data Analytics TF: State data for 53 (+6) states/territories are integrated into the HHS GeoHEALTH Common Operating Picture (COP) to support decision making policy actions on such measures as stay at home/shelter in place orders, school closures, and declaration of

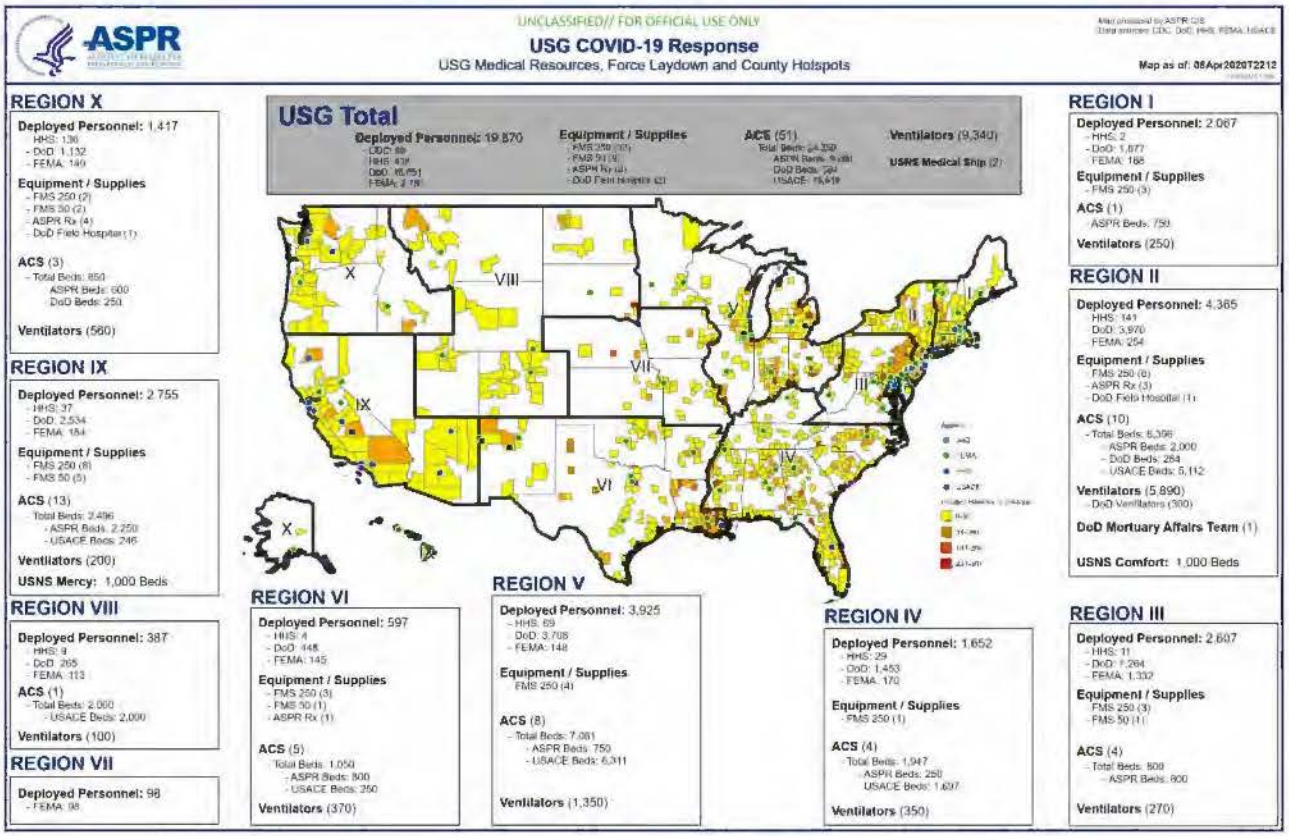
state of emergency. Produced model that shows the estimated impacts of different mitigation measure decisions

- Healthcare Resiliency TF: Focus is on utilization systems; focusing on Batelle decontamination solution method for cleaning and re-using PPE, a method that could decontaminate 80,000 masks per day

- Laboratory Diagnostics TF: Piloted the online data collection form for hospitals to submit daily testing data in a simplified format; Shipped RT-PCR testing reagents to Los Alamos and Pacific Northwest National Laboratories to begin validation testing of alternative extraction methods

- MCM TF: Highlighted new ORCHID clinical study: study to evaluate hydroxychloroquine for COVID-19; 10 of 510 patients enrolled; continuing to enroll patients in other studies. USG funded clinical studies:
    - Therapeutics: 4 Phase 3 trials
    - Vaccines: 2 Phase 1 trials
    - Observational Natural History Study

- Supply Chain TF: 4 new Airbridge flights arrived April 8; DoD is developing a broader and longer-term strategy involving switching partially or entirely, depending on the need, to a maritime bridge rather than the air bridge



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What We Are Doing

- RI: The state intends to use the Federally provided testing machines to support low volume testing at respiratory clinic and mobile settings for demographics who are unable to travel to testing sites
- CBTS TF: Extensions of federal management being processed for sites in New Jersey, Texas, Louisiana, and possibly Illinois and Florida;
- Community Mitigation TF: developing outline for frequently asked questions on children and youth with special health care needs with HRSA; developing a plan for indicators and thresholds that a community or state can just when they start to lift CMM and the plan for how that should move forward
- Data Analytics TF: Modeling ICU and vent cases over time of outbreak to support MCM task force in how many doses of treatment will be necessary throughout outbreak
- Healthcare Resilience TF: PPE Preservation workgroup is finalizing the key performance indicators for Battelle to report production output, impact of decontaminated N-95 respirators per day
- Laboratory Diagnostics TF: Continuing to support stocking of IRR with diagnostic supplies, including the movement of 210 extraction kits (250 tests per kit) for state Public Health Labs; developing testing strategy to get people back to work safely; working to alleviate testing supply bottlenecks
- Supply Chain TF: Resource Prioritization Cell will publish Bulletin #2 with recommendations for PPE, Extraction Kits (Pharmaceuticals), and Battelle N95 Sterilization Systems by geographic areas for NRCC and Resource Support Section allocation decision making. This list will update Appendix B of all MOAs with partnering distributors to provide direction for resource distribution to federal priorities

US CASE COUNTS & OUTBREAK UPDATES

- 430,091 [+32,518] cases and 14,794 [+1,900] deaths
- 7,513 U.S. healthcare workers COVID positive (128 travel related, 1,376 contact with known case, 6,009 under investigation) and 25 deaths (11 CA, 4 LA, 6 NY, 1 KS, 1 MA, 1 WA, 1 PA) – *per CDC report, update was not available by reporting deadline*
- **Domestic outbreaks, widespread**:
  - 50 states + DC, Guam, PR, USVI, and CNMI have cases
  - 8 states have over 5,000 cases and 9 states have over 15,000. NY has 151,473 cases (including 81,803 in NYC (54% of the state total) representing 35% of all US cases
- **International outbreaks, widespread:**
  - There were 73,639 new cases and 6,695 new deaths in the last 24 hours. PAHO region accounted for 45% and Europe accounted for 46% of the reported new cases

From: West, Lauren R. <LRWEST@mgh.harvard.edu>

To: 'Raabe, Vanessa' <Vanessa.Raabe@nyulangone.org>;
'McLellan, Susan' <sumclell@utmb.edu>

CC: 'Vasistha, Sami' <sami.vasistha@unmc.edu>;
'Kraft, Colleen S' <colleen.kraft@emory.edu>;
'Levine, Corri B.' <cblevine@utmb.edu>;
'Aneesh Mehta' <aneesh.mehta@emory.edu>;
'Cabada, Miguel' <micabada@utmb.edu>;
'ashane@emory.edu' <ashane@emory.edu>;
'Boulter, Kathleen C' <KBoulter@nebraskamed.com>;
(b)(6)@gmail.com' <(b)(6)@gmail.com>;
'Caroline.Croyle@dhha.org' <Caroline.Croyle@dhha.org>;
'Larson, LuAnn' <llarson@unmc.edu>;
'Lowe, John-martin J' <jjlowe@unmc.edu>;
'ahmed.babiker@emory.edu' <ahmed.babiker@emory.edu>;
'jennifer.garland@cshs.org' <jennifer.garland@cshs.org>;
'Kortepeter, Mark G' <mark.kortepeter@unmc.edu>;
'sandra.ockers@emoryhealthcare.org' <sandra.ockers@emoryhealthcare.org>;
'jonathan.grein@cshs.org' <jonathan.grein@cshs.org>;
Davey, Richard (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=967b9cf65222492fb885fc8730daa04e-richard.dav <rdavey@niaid.nih.gov>;
'henry.m.wu@emory.edu' <henry.m.wu@emory.edu>;
'Susan Kline' <kline003@umn.edu>;
Fagan, Ryan (CDC/DDID/NCEZID/DHQP) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1cac11c087c34253b0988e94a2020ef8-Fagan, Ryan <fev3@cdc.gov>;
'jay.varkey@emory.edu' <jay.varkey@emory.edu>;
'Brett-Major, David M' <david.brettmajor@unmc.edu>;
'Hewlett, Angela L' <alhewlett@unmc.edu>;
'marybeth.sexton@emory.edu' <marybeth.sexton@emory.edu>;
'nahid.bhadelia@bmc.org' <nahid.bhadelia@bmc.org>;
'josia.mamora@emoryhealthcare.org' <josia.mamora@emoryhealthcare.org>;
'SALEXAN1@Fairview.org' <SALEXAN1@fairview.org>;
'Caitlin Rivers' <crivers6@jhu.edu>;
'Vasa, Angela M' <AVASA@nebraskamed.com>;
'Bell, Sonia A' <sabell@emory.edu>;
'Grindle, Amanda' <Amanda.Grindle@choa.org>;
'Maria.Frank@dhha.org' <Maria.Frank@dhha.org>;
'Claudia.flores@providence.org' <Claudia.flores@providence.org>;
'Kratochvil, Christopher J' <ckratoch@unmc.edu>;
Beigel, John (NIH) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=45af28983cfa4300b0217b591151861c-john.beigel <jbeigel@niaid.nih.gov>;
'Micheels, Teresa A' <tmicheels@nebraskamed.com>;
'Cieslak, Theodore J' <ted.cieslak@unmc.edu>;
'Broadhurst, Mara J' <jana.broadhurst@unmc.edu>;
'Lauren Sauer' <lsauer2@jhmi.edu>;
'Boer0039@umn.edu' <Boer0039@umn.edu>;
'Hovorka, Tina' <thovorka@unmc.edu>;
'Christa.Arguinchona@providence.org' <Christa.Arguinchona@providence.org>;
'Ribner, Bruce' <bribner@emory.edu>;
'Dierberg, Kerry' <Kerry.Dierberg@nyulangone.org>;
'Jared.Evans@jhuapl.edu' <Jared.Evans@jhuapl.edu>;
'Levy, Deborah A' <deborah.levy@unmc.edu>;
'andrea.echeverri@nychhc.org' <andrea.echeverri@nychhc.org>;
Uyeki, Timothy M. (CDC/DDID/NCIRD/ID) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=781bd33db3a543d3845be279f7e085c7-Uyeki, Timo <tmu0@cdc.gov>;
Palmore, Tara (NIH/CC/OD) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=79fe7e14d84c4a4cb6c6a6b53f108b95-tara.palmor <tpalmore@cc.nih.gov>;
'Blanton, Lucas S.' <lsblanto@utmb.edu>;
'Vanairsdale, Sharon' <sharon.vanairsdale@emory.edu>;
Shenoy, Erica Seiguer,M.D.,Ph.D. <ESHENOY@mgh.harvard.edu>;

'Schwedhelm, Michelle M' <SSchwedh@nebraskamed.com>;
'Marshall Lyon' <gmlyon@emory.edu>;
'Ntiforo, Corrie' <contifor@utmb.edu>;
'Seashore, Justin' <juseasho@utmb.edu>;
'henry.arguinchona@providence.org' <henry.arguinchona@providence.org>;
Hunt, Richard (OS/ASPR/EMMO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a104469df5184cc38bf02034af7eca04-Hunt, Richa <Richard.Hunt@hhs.gov>;
Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>;
Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>;
Marston, Hilary (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=93be476c17024bbcbc5b44add01fe6a8-hilary.mars <hilary.marston@nih.gov>;
Lane, Cliff (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=11a174ee688e426392d98ba9cd5e1945-cliff.lane. <clane@niaid.nih.gov>;
Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>;
Risi, George (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ebacebdbbbc040c6afe53c5ecc90e56d-Risi, Georg <George.Risi@hhs.gov>;
'Mukherjee, Vikramjit' <Vikramjit.Mukherjee@nyulangone.org>;
Gandhi, Rajesh Tim,M.D. <RGANDHI@mgh.harvard.edu>

Subject: RE: Corona Call

Date: 2020/03/11 14:07:40

Priority: Normal

Type: Note

Adding Raj Gandhi to this discussion, a MGH ID physician.

From: Raabe, Vanessa [mailto:Vanessa.Raabe@nyulangone.org]
Sent: Wednesday, March 11, 2020 11:35 AM
To: McLellan, Susan
Cc: Vasistha, Sami; Kraft, Colleen S; Levine, Corri B.; Aneesh Mehta; Cabada, Miguel; West, Lauren R.; ashane@emory.edu; Boulter, Kathleen C; [redacted]@gmail.com; Caroline.Croyle@dhha.org; Larson, LuAnn; Lowe, John-martin J; ahmed.babiker@emory.edu; jennifer.garland@cshs.org; Kortepeter, Mark G; sandra.ockers@emoryhealthcare.org; jonathan.grein@cshs.org; RDAVEY@niaid.nih.gov; henry.m.wu@emory.edu; Susan Kline; fev3@cdc.gov; jay.varkey@emory.edu; Brett-Major, David M; Hewlett, Angela L; marybeth.sexton@emory.edu; nahid.bhadelia@bmc.org; josia.mamora@emoryhealthcare.org; SALEXAN1@Fairview.org; Caitlin Rivers; Vasa, Angela M; Bell, Sonia A; Grindle, Amanda; Maria.Frank@dhha.org; Claudia.flores@providence.org; Kratochvil, Christopher J; jbeigel@niaid.nih.gov; Micheels, Teresa A; Cieslak, Theodore J; Broadhurst, Mara J; Lauren Sauer; Boer0039@umn.edu; Hovorka, Tina; Christa.Arguinchona@providence.org; Ribner, Bruce; Dierberg, Kerry; Jared.Evans@jhuapl.edu; Levy, Deborah A; andrea.echeverri@nychhc.org; tmu0@cdc.gov; tpalmore@cc.nih.gov; Blanton, Lucas S.; Vanairsdale, Sharon; Shenoy, Erica Seiguer,M.D.,Ph.D.; Schwedhelm, Michelle M; Marshall Lyon; Ntiforo, Corrie; Seashore, Justin; henry.arguinchona@providence.org; Hunt, Richard (OS/ASPR/EMMO); Rick.Bright@hhs.gov; Gary.Disbrow@hhs.gov; hilary.marston@nih.gov; clane@niaid.nih.gov; robert.walker@hhs.gov;

george.risi@hhs.gov; Mukherjee, Vikramjit
Subject: Re: Corona Call

External Email - Use Caution

Chloroquine is in limited supply in the US unfortunately despite better worldwide availability. hydroxychloroquine is easier to find and recent in vitro paper suggests lower concentrations needed to inhibit replication with HCQ compared to CQ.

We are starting to see some of our providers using kaletra in our COVID-19 patients in NY. Will be great when our approvals are through to get these folks enrolled in RCT!

Vanessa
Sent from my iPhone

On Mar 11, 2020, at 10:29 AM, McLellan, Susan <sumclell@utmb.edu>wrote:

[EXTERNAL]

Some of my colleagues (including our CMO) are getting excited about chloroquine. Comments anyone? (and yes I am really fighting for the concept of stick to RCTs!)
Susan

Susan McLellan MD MPH
Infectious Diseases
UTMB
Sent from my iPhone, so please forgive any lax spelling, grammar, or etiquette

On Mar 6, 2020, at 3:05 PM, Vasistha, Sami <sami.vasistha@unmc.edu>wrote:

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If you are having issues connecting through the zoom link, please dial in
Phone one-tap: US: (b)(6)

Sami Vasistha
Program Manager
National Ebola Training and Education Center
Global Center for Health Security

University of Nebraska Medical Center
986161 Omaha, NE 68198-6161
Desk: (402)559-0550 Cell: (b)(6)
Sami.vasistha@unmc.edu
<image001.png>

Sender: West, Lauren R. <LRWEST@mgh.harvard.edu>

Recipient:
'Raabe, Vanessa' <Vanessa.Raabe@nyulangone.org>;
'McLellan, Susan' <sumclell@utmb.edu>;
'Vasistha, Sami' <sami.vasistha@unmc.edu>;
'Kraft, Colleen S' <colleen.kraft@emory.edu>;
'Levine, Corri B.' <cblevine@utmb.edu>;
'Aneesh Mehta' <aneesh.mehta@emory.edu>;
'Cabada, Miguel' <micabada@utmb.edu>;
'ashane@emory.edu' <ashane@emory.edu>;
'Boulter, Kathleen C' <KBoulter@nebraskamed.com>;
(b)(6)@gmail.com' (b)(6)@gmail.com>;
'Caroline.Croyle@dhha.org' <Caroline.Croyle@dhha.org>;
'Larson, LuAnn' <llarson@unmc.edu>;
'Lowe, John-martin J' <jjlowe@unmc.edu>;
'ahmed.babiker@emory.edu' <ahmed.babiker@emory.edu>;
'jennifer.garland@cshs.org' <jennifer.garland@cshs.org>;
'Kortepeter, Mark G' <mark.kortepeter@unmc.edu>;
'sandra.ockers@emoryhealthcare.org' <sandra.ockers@emoryhealthcare.org>;
'jonathan.grein@cshs.org' <jonathan.grein@cshs.org>;
Davey, Richard (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=967b9cf65222492fb885fc8730daa04e-richard.dav <rdavey@niaid.nih.gov>;
'henry.m.wu@emory.edu' <henry.m.wu@emory.edu>;
'Susan Kline' <kline003@umn.edu>;
Fagan, Ryan (CDC/DDID/NCEZID/DHQP) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1cac11c087c34253b0988e94a2020ef8-Fagan, Ryan <fev3@cdc.gov>;
'jay.varkey@emory.edu' <jay.varkey@emory.edu>;
'Brett-Major, David M' <david.brettmajor@unmc.edu>;
'Hewlett, Angela L' <alhewlett@unmc.edu>;
'marybeth.sexton@emory.edu' <marybeth.sexton@emory.edu>;
'nahid.bhadelia@bmc.org' <nahid.bhadelia@bmc.org>;
'josia.mamora@emoryhealthcare.org' <josia.mamora@emoryhealthcare.org>;
'SALEXAN1@Fairview.org' <SALEXAN1@fairview.org>;
'Caitlin Rivers' <crivers6@jhu.edu>;
'Vasa, Angela M' <AVASA@nebraskamed.com>;
'Bell, Sonia A' <sabell@emory.edu>;
'Grindle, Amanda' <Amanda.Grindle@choa.org>;
'Maria.Frank@dhha.org' <Maria.Frank@dhha.org>;
'Claudia.flores@providence.org' <Claudia.flores@providence.org>;

	'Kratochvil, Christopher J' <ckratoch@unmc.edu>; Beigel, John (NIH) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=45af28983cfa4300b0217b591151861c-john.beigel <jbeigel@niaid.nih.gov>; 'Micheels, Teresa A' <tmicheels@nebraskamed.com>; 'Cieslak, Theodore J' <ted.cieslak@unmc.edu>; 'Broadhurst, Mara J' <jana.broadhurst@unmc.edu>; 'Lauren Sauer' <lsauer2@jhmi.edu>; 'Boer0039@umn.edu' <Boer0039@umn.edu>; 'Hovorka, Tina' <thovorka@unmc.edu>; 'Christa.Arguinchona@providence.org' <Christa.Arguinchona@providence.org>; 'Ribner, Bruce' <bribner@emory.edu>; 'Dierberg, Kerry' <Kerry.Dierberg@nyulangone.org>; 'Jared.Evans@jhuapl.edu' <Jared.Evans@jhuapl.edu>; 'Levy, Deborah A' <deborah.levy@unmc.edu>; 'andrea.echeverri@nychhc.org' <andrea.echeverri@nychhc.org>; Uyeki, Timothy M. (CDC/DDID/NCIRD/ID) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=781bd33db3a543d3845be279f7e085c7-Uyeki, Timo <tmu0@cdc.gov>; Palmore, Tara (NIH/CC/OD) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=79fe7e14d84c4a4cb6c6a6b53f108b95-tara.palmor <tpalmore@cc.nih.gov>; 'Blanton, Lucas S.' <lsblanto@utmb.edu>; 'Vanairsdale, Sharon' <sharon.vanairsdale@emory.edu>; Shenoy, Erica Seiguer,M.D.,Ph.D. <ESHENOY@mgh.harvard.edu>; 'Schwedhelm, Michelle M' <SSchwedh@nebraskamed.com>; 'Marshall Lyon' <gmlyon@emory.edu>; 'Ntiforo, Corrie' <contifor@utmb.edu>; 'Seashore, Justin' <juseasho@utmb.edu>; 'henry.arguinchona@providence.org' <henry.arguinchona@providence.org>; Hunt, Richard (OS/ASPR/EMMO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=a104469df5184cc38bf02034af7eca04-Hunt, Richa <Richard.Hunt@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Marston, Hilary (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=93be476c17024bbcbc5b44add01fe6a8-hilary.mars <hilary.marston@nih.gov>; Lane, Cliff (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=11a174ee688e426392d98ba9cd5e1945-cliff.lane. <clane@niaid.nih.gov>; Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>; Risi, George (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ebacebdbbbc040c6afe53c5ecc90e56d-Risi, Georg <George.Risi@hhs.gov>; 'Mukherjee, Vikramjit' <Vikramjit.Mukherjee@nyulangone.org>; Gandhi, Rajesh Tim,M.D. <RGANDHI@mgh.harvard.edu>
Sent Date:	2020/03/11 14:07:16
Delivered Date:	2020/03/11 14:07:40

From:	Thomas Kleen <tk@immodulon.com>
To:	Fauci, Anthony (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=826965b24a314ffca7eddcb6e8229aa7-anthony.fau <afauci@niaid.nih.gov>; Donabedian, Armen (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1c83127c6669486888ec57ccc0d09c28-Donabedian, <armen.donabedian@hhs.gov>; Zarrabian, Amanda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0c650b07917242129deb0f942bb4cc10-Zarrabian, <amanda.zarrabian@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	Proven safe inhalation of nebulized Hydroxychloroquine (HCQ) could overcome safety and efficacy concerns of oral HCQ
Date:	2020/04/28 05:49:40
Priority:	Normal
Type:	Note

Dear Tony, Armen, Rick and Amanda,

I hope this email finds you well. I and very aware that there is so much controversy about HCQ and CQ in COVID-19 and several proper clinical trials will finally start. My concern is that oral dosing may not be appropriate in the COVID-19 setting. Therefore I am reaching out to you with a, not new, scientifically based hypothesis for using nebulized Hydroxychloroquine (HCQ) inhalation in your clinical studies as treatment for COVID-19 patients. This approach can be based on already available clinical safety data, and there appears to be no IP hurdles to such use. Furthermore, no special or proprietary devices would be needed to use it in that manner, only standard, widely available, medical nebulizers.

Please allow me to explain:

- • The attached 2003 patent US6572858B1 is expired, fee related. In any case, it appears that it will definitively expire within a few days on 2020-05-01
- • The lapsed patent already describes animal safety data and identifies dosing for nebulized Hydroxychloroquine (HCQ) inhalation (patent is attached, and important sections are highlighted)
- • The former owner of the patent rights APT Pharmaceuticals, Inc. (Inactive) in 2004 made a public disclosure about the potential of aerosolized HCQ potentially being effective in SARS-CoV (press release from 2004 is attached and the relevant text highlighted)
- • APT (inactive) with their partner Aradigm Corporation (filed for protection under Chapter 11 in the USA on 2019-02-15) took the program on inhaled HCQ in Asthma from Phase 1 to Phase 2a data, where it failed on efficacy endpoints, and it appears, not

because of safety concerns (2006 Aradigm annual report is attached with the respective disclosure highlighted)

- • You all are very aware of the respective literature and data suggesting HCQ efficacy *in vitro* against SARS-CoV-2 and the conflicting, anecdotal data about potential efficacy in off label use in SARS-CoV-2 patients and COVID-19
- • Novartis already announced it will carry out a Phase 3 trial assessing standard, oral use of HCQ as a treatment for hospitalized patients with COVID-19 in a randomized, double-blind, placebo controlled study, which will recruit approximately 440 patients and use a supply of HCQ to be donated by Novartis' Sandoz generics and biosimilars division
- • It is known that typical oral HCQ use is characterized by a significant delay in the onset of the anti-malarial action, due to the need to reach active concentrations of the therapeutic agent in certain organs
- • For the lungs, being one of the target organs in COVID-19, inhalation would shortcut the time it takes for enough drug to build up via transfer from the intestines into the blood to finally reach the lungs in sufficient concentration
- • Application of oral HCQ to later stage COVID-19 may face additional hurdles of bioavailability in the lung because vascular defects caused by inflammation, infection, micro blood clots and high fluid pressure in the lungs
- • Rapid achievement of a minimum effective dose against SARS-CoV-2 in the lungs could be especially relevant to Novartis' Phase 3 trial, since it appears to focus on already hospitalized patients with COVID-19 and more severe sick patients, late in the disease and overall peak replicative cycle of SARS-CoV-2
- • I do not have access to the dosing of the APT/Aradigm Phase1 and Phase 2 inhaled HCQ studies, but US6572858B1 discloses that it is preferred that the drug is administered locally at a dosage of up 2 mg/kg animal weight, as effective and safe and preferably from about 0.200 to about 0.650 mg/kg animal weight
- • For a 70kg individual, that translates to about 50mg to 140mg, which appears to safe dosing for inhalation
- • If effective against SARS-CoV-2 as well, these much lower than currently used doses, should greatly diminish the risk of serious side effects observed with high dose HCQ use, e.g. retinal damage and cardio QT prolongation, arrhythmia and death

I would like to emphasize that neither me personally nor my employer have any financial stake or interest in the use of nebulized Hydroxychloroquine (HCQ) inhalation in COVID-19. The above suggestions are solely based on my personal perceived scientific and medical rationale with the public information available to me. They have not been independently verified. The opinions and theories brought forward here are my own and not officially endorsed by my employer.

I still hope that this information may prove useful to you and your goals by using HCQ to treat patients with high unmet medical need and providing hope during the pandemic.

Thank you for your consideration and kind regards,

Thomas

Dr. Thomas-Oliver Kleen, Ph.D.
Chief Scientific Officer

Immodulon Therapeutics Ltd
| 6-9 The Square, Stockley Park, Uxbridge UB11 1FW, United Kingdom |
| Tel: +44 20 3137 6346 | Fax: +44 20 8929 9283 | tk@immodulon.com |

Sender:	Thomas Kleen <tk@immodulon.com>
Recipient:	Fauci, Anthony (NIH/NIAID) [E] /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=826965b24a314ffca7eddcb6e8229aa7-anthony.fau <afauci@niaid.nih.gov>; Donabedian, Armen (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1c83127c6669486888ec57ccc0d09c28-Donabedian, <armen.donabedian@hhs.gov>; Zarrabian, Amanda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0c650b07917242129deb0f942bb4cc10-Zarrabian, <amanda.zarrabian@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Sent Date:	2020/04/28 05:48:55
Delivered Date:	2020/04/28 05:49:40
Message Flags:	Unread

APT Starts Human Trials of Aerosolized Hydroxychloroquine for Asthma

9.13.2004

Tucson, Ariz. – Sep 13, 2004

APT Pharmaceuticals is beginning clinical studies of aerosolized hydroxychloroquine (AHCQ) for treatment of respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), rhinitis and severe acute respiratory syndrome (SARS).

Hydroxychloroquine is best known as a treatment for malaria, but the drug is also classified as a slow-onset disease-modifying antirheumatic drug (DMARD) administered in tablet form as a first-line therapy for systemic lupus erythematosus, rheumatoid arthritis and sarcoidosis. APT's patented technology is based on targeted administration of amino quinolines to inflamed tissues. APT's proprietary aerosolized dosage forms and routes of administration achieve a faster onset of action and greater therapeutic effect than conventional oral therapy, and at substantially lower systemic doses. The company believes targeted delivery of hydroxychloroquine will be a highly effective and safer alternative to corticosteroid treatments.

APT starts human safety and tolerability studies of AHCQ today in Australia and plans to begin Phase II studies in asthmatics in the first quarter of 2005. These studies will use the advanced AERx® pulmonary delivery system by Aradigm Corporation of Hayward, Calif., which is designed to maximize drug delivery in a patient-friendly format.

"The goal of the first study is to establish safety parameters of this new route of administration and dosage form in order to set the stage for efficacy studies in diseases such as asthma, COPD and SARS," said APT President Gino Di Sciullo, Ph.D. "AHCQ offers the prospect of achieving antiviral and anti-inflammatory therapeutic effects within hours rather than the weeks to months needed in current oral dosing of hydroxychloroquine."

APT has collaborated with researchers from leading academic centers in the United States and Canada to investigate the benefit of AHCQ on respiratory viral infections.

"Laboratory studies have demonstrated that hydroxychloroquine inhibits both the transmission and the inflammatory responses of human airway cells to the common cold virus (human rhinovirus)," said B. Lauren Charous, M.D., director of the Allergy and Respiratory Care Center at Advanced Healthcare in Milwaukee, who is scientific adviser to APT. "We are encouraged that the levels needed to block the virus can be achieved by aerosolized delivery. The combined anti-inflammatory and antiviral activities of AHCQ have the potential to create a new product category for treatment of pulmonary inflammation."

This summer, with funding from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, Dale Barnard, Ph.D., at the Institute for Anti-Viral Research at Utah State University in Logan, completed initial laboratory studies showing hydroxychloroquine inhibits SARS-associated corona virus (SARS-CoV) at similar low concentrations. These results with hydroxychloroquine were corroborated recently in findings reported by Marc Van Ranst, Ph.D., a virologist at the Rega Institute for Medical Research in Belgium. He and his colleagues found that chloroquine, a closely related drug, is also effective at inhibiting SARS-CoV in vitro. NIAID is supporting further studies by Barnard of hydroxychloroquine in an animal model. These studies are currently underway.

Research Corporation Technologies (RCT) in Tucson, Ariz., founded APT Pharmaceuticals to advance development of the AHCQ technology. As the primary investor, RCT funded early formulation work, efficacy studies, preclinical safety studies and continues its support of these clinical trials. U.S. Patent No. 6,572,858 and other pending worldwide patent applications protect the APT technology.

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Research Corporation Technologies
6440 N. Swan Road, Suite 200
Tucson, AZ 85718
(520) 748-4400 • rctinfo@rctech.com

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(12) **United States Patent**
Charous

(10) **Patent No.: US 6,572,858 B1**
(45) **Date of Patent: Jun. 3, 2003**

(54) **USES FOR ANTI-MALARIAL THERAPEUTIC AGENTS**

(75) Inventor: **B. Lauren Charous**, Fox Point, WI (US)

(73) Assignee: **APT Pharmaceuticals, LLC**, Tucson, AZ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/563,267**

(22) Filed: **May 1, 2000**

Related U.S. Application Data

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(51) **Int. Cl.**[7] **A61K 39/00**; A61K 39/38; A61K 45/00; A01N 61/00

(52) **U.S. Cl.** **424/184.1**; 424/278.1; 424/279.1; 514/1

(58) **Field of Search** 424/1.13, 174.1, 424/184.1, 278.1, 279.1; 514/1

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Primary Examiner—Mark Navarro
(74) *Attorney, Agent, or Firm*—Scully, Scott, Murphy & Presser

(57) **ABSTRACT**

A diversity of inflammatory diseases can be treated via local delivery to the patient of a composition containing a therapeutically effective amount of an anti-malarial agent. In a preferred embodiment of the method of the invention, a pulmonary inflammatory condition, such as asthma, is treated by inhalation of an aerosolized anti-malarial agent, such as hydroxychloroquine.

9 Claims, 10 Drawing Sheets

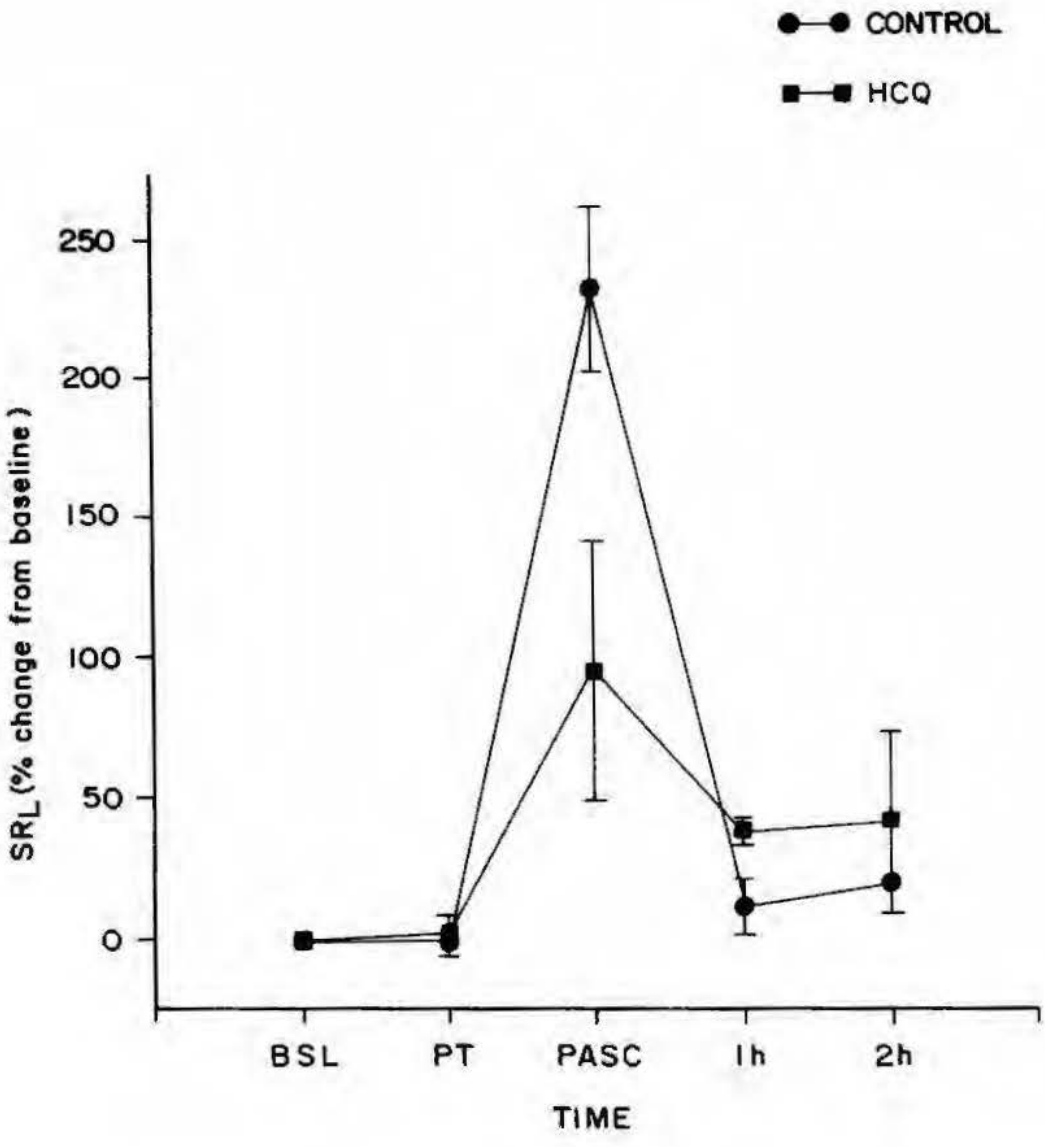

CONTROL
HCQ
250
200
150
100
50
0
SRL (% change from baseline)
BSL
PT
PASC
1h
2h
TIME

FIG. 1

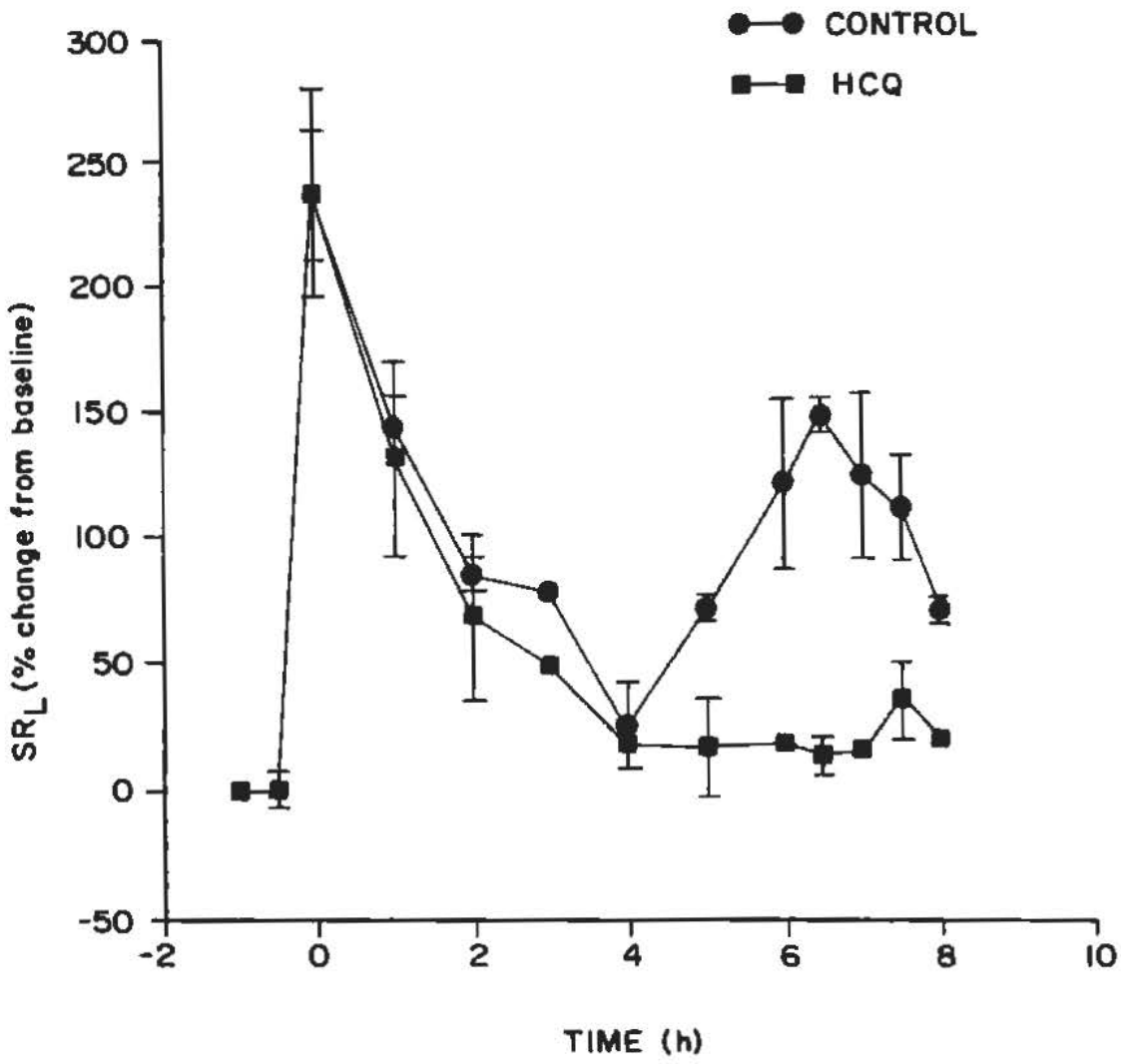

CONTROL
HCQ
300
250
200
150
100
50
0
-50
-2
0
2
4
6
8
10
SR_L (% change from baseline)
TIME (h)

FIG. 2

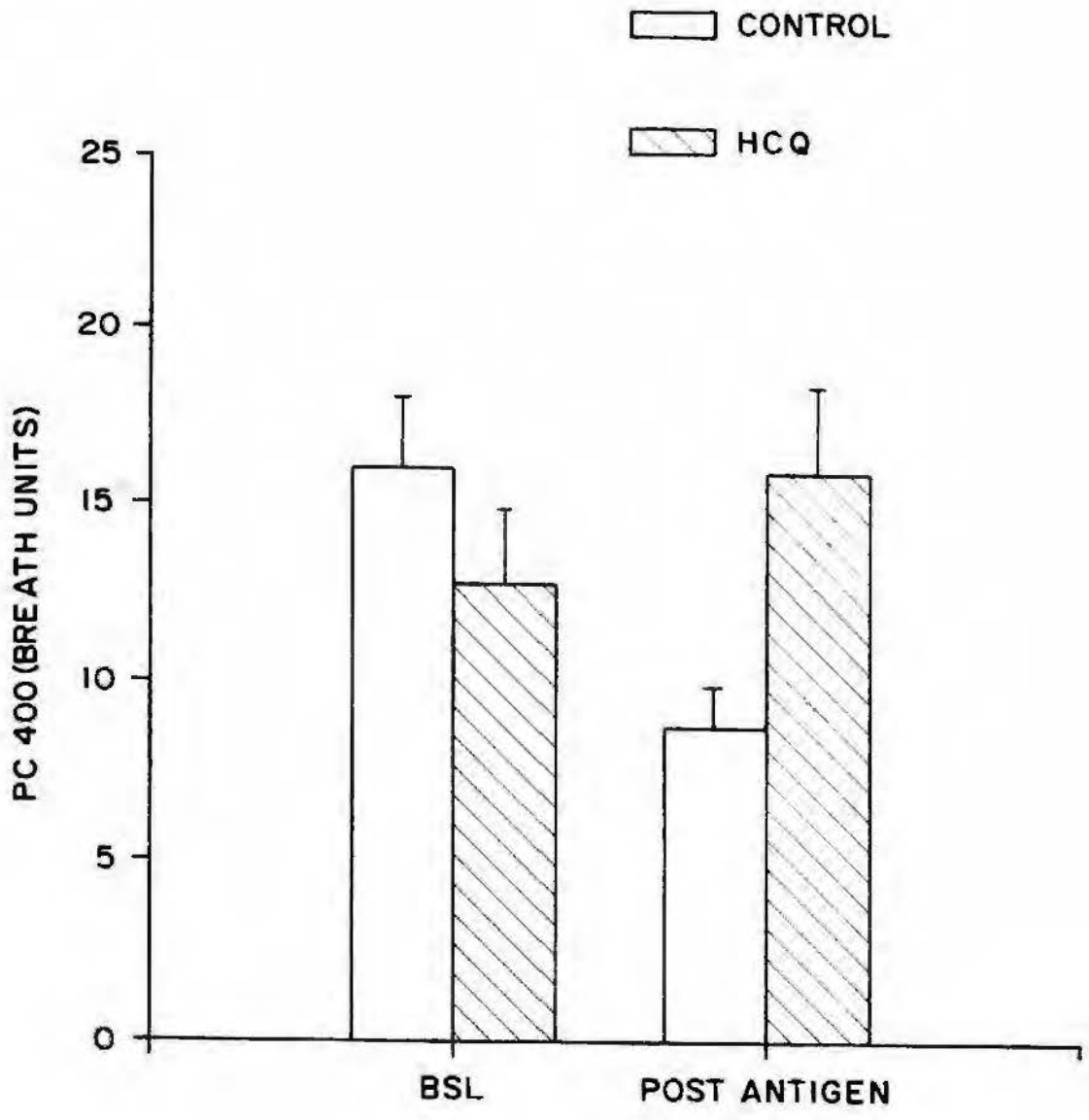

CONTROL
HCQ
25
20
15
10
5
0
PC 400 (BREATH UNITS)
BSL
POST ANTIGEN

FIG. 3

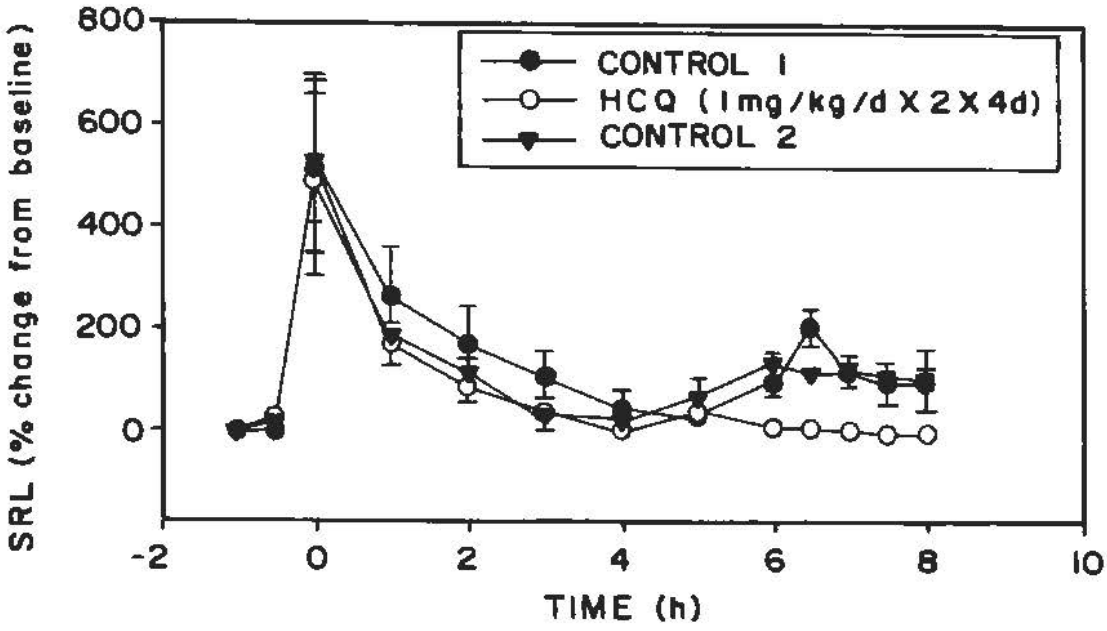

SRL (% change from baseline)
800
600
400
200
0
-2
0
2
4
6
8
10
TIME (h)
CONTROL 1
HCQ (1mg/kg/d X 2X 4d)
CONTROL 2

FIG.4A

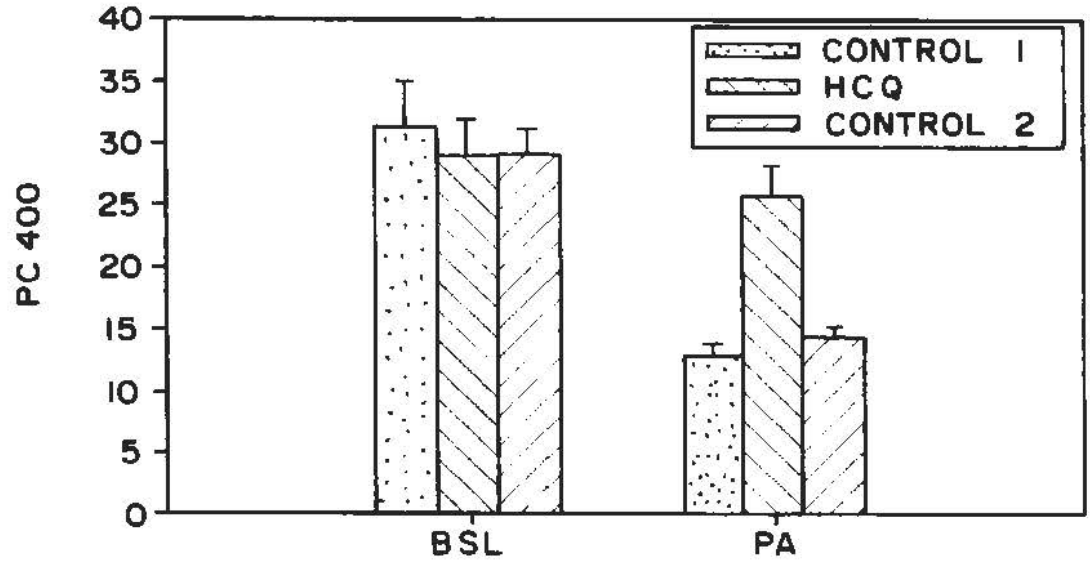

PC 400
40
35
30
25
20
15
10
5
0
BSL
PA
CONTROL 1
HCQ
CONTROL 2

FIG.4B

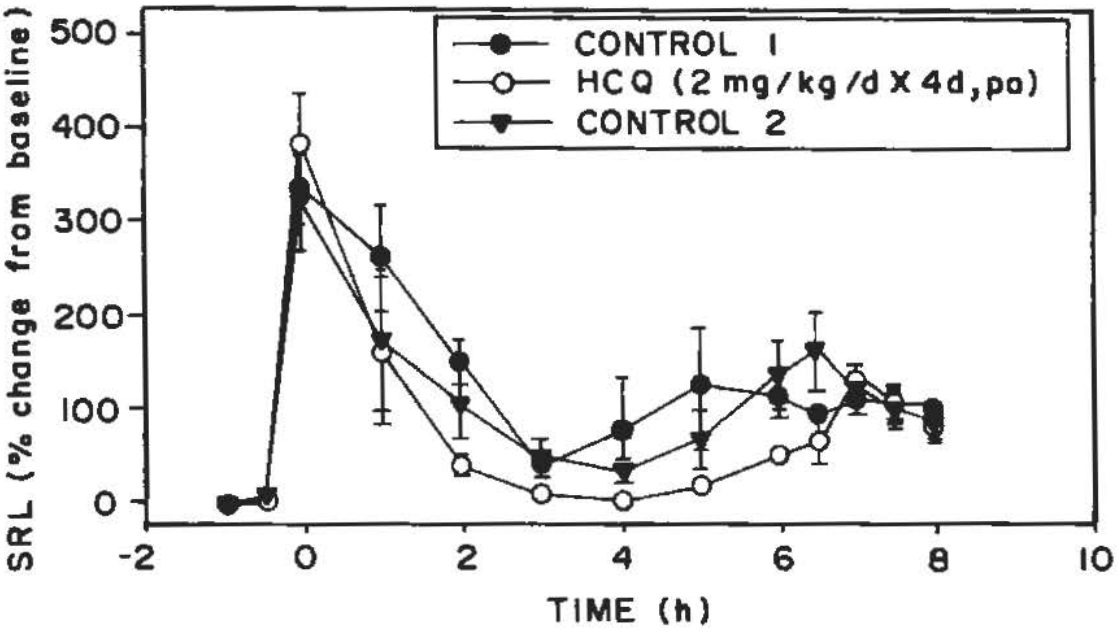

CONTROL 1
HCQ (2 mg/kg/d X 4d, po)
CONTROL 2
SRL (% change from baseline)
500
400
300
200
100
0
-2
0
2
4
6
8
10
TIME (h)

FIG. 5A

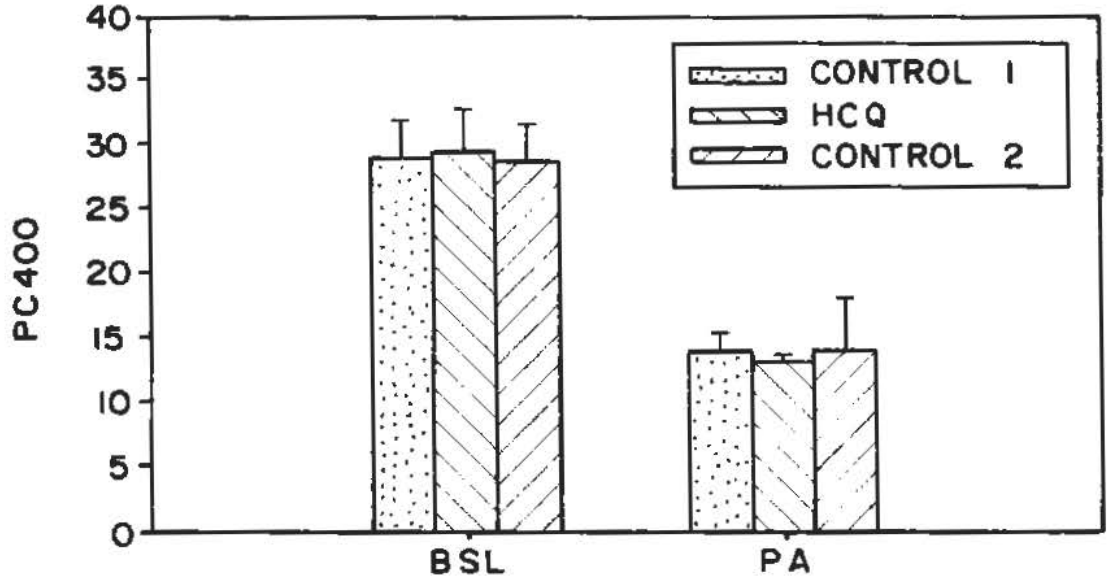

CONTROL 1
HCQ
CONTROL 2
PC400
40
35
30
25
20
15
10
5
0
BSL
PA

FIG. 5B

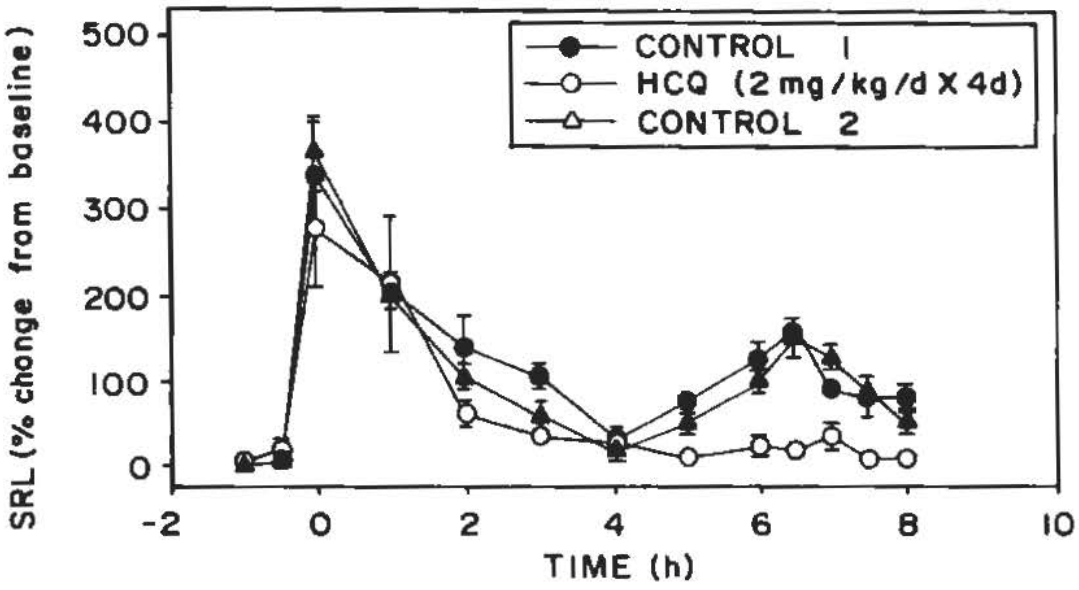

CONTROL 1
HCQ (2 mg/kg/d X 4d)
CONTROL 2
SRL (% change from baseline)
500
400
300
200
100
0
-2
0
2
4
6
8
10
TIME (h)

FIG. 6A

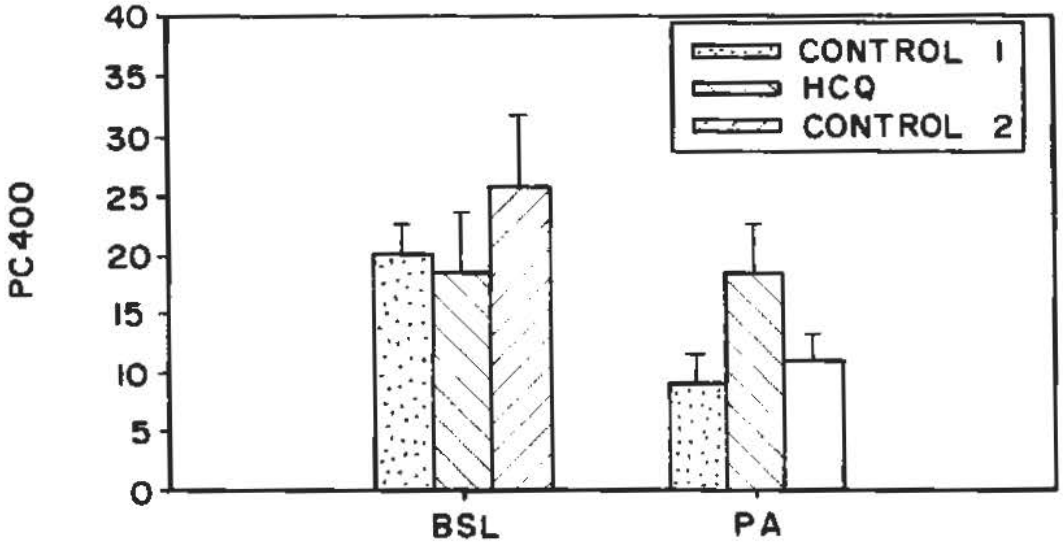

CONTROL 1
HCQ
CONTROL 2
PC400
40
35
30
25
20
15
10
5
0
BSL
PA

FIG. 6B

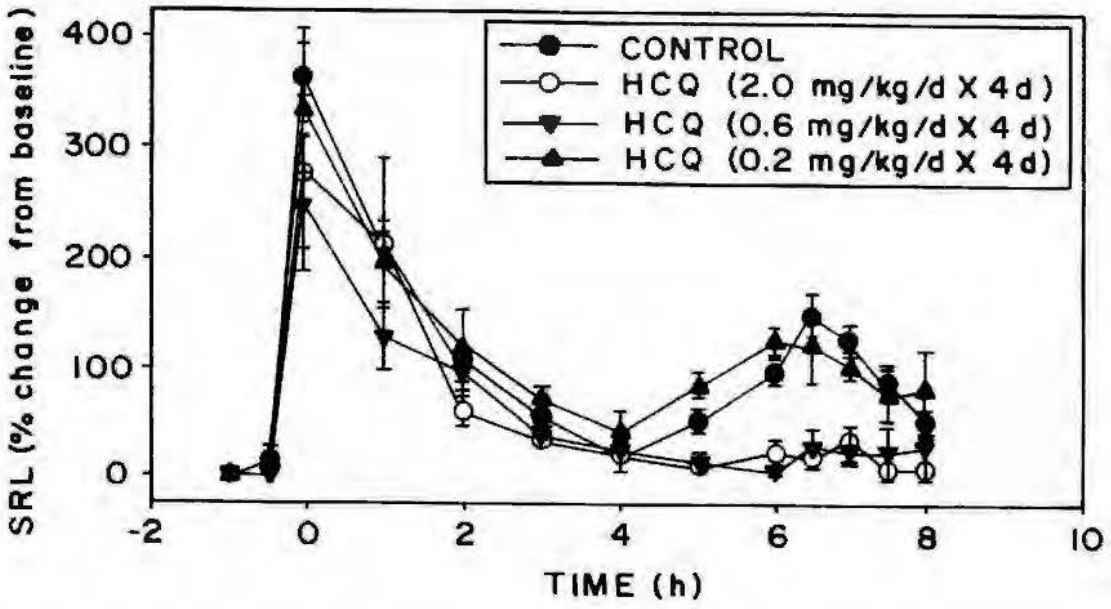


FIG. 7A

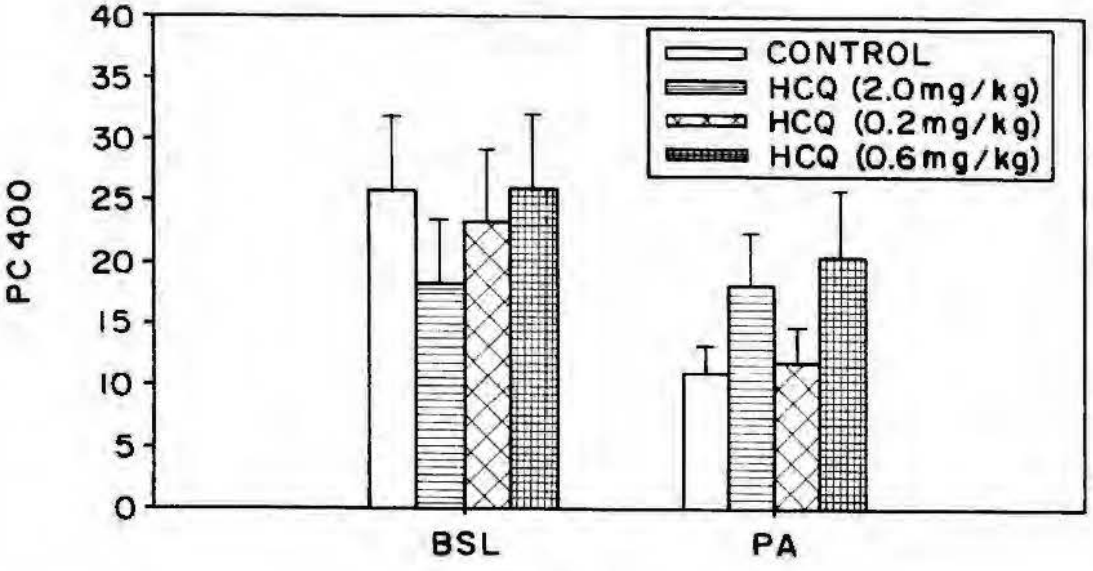


FIG. 7B

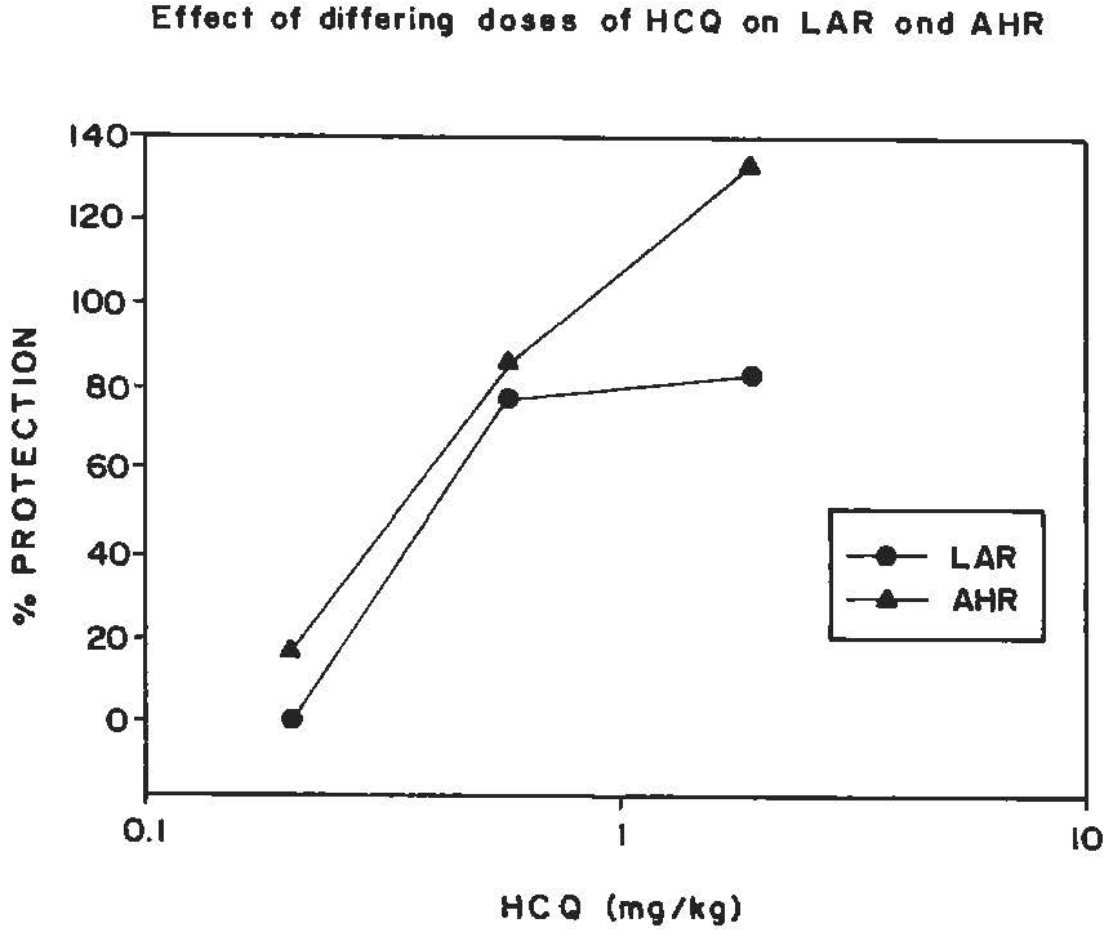

Effect of differing doses of HCQ on LAR ond AHR
% PROTECTION
140
120
100
80
60
40
20
0
0.1
1
10
HCQ (mg/kg)
LAR
AHR

FIG. 8

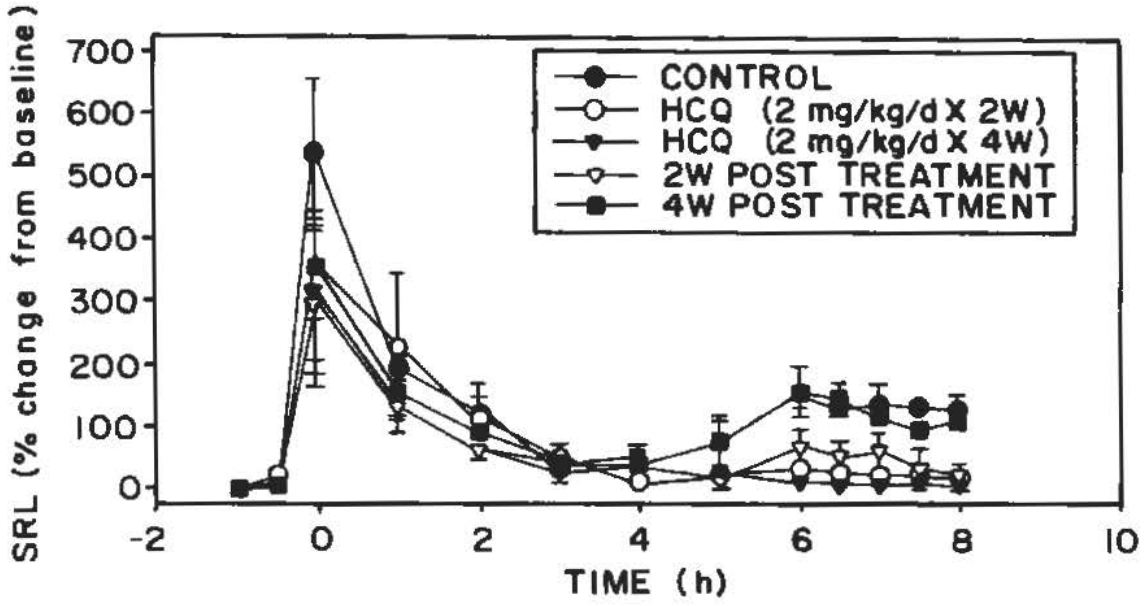

SRL (% change from baseline)
700
600
500
400
300
200
100
0
-2
0
2
4
6
8
10
TIME (h)
CONTROL
HCQ (2 mg/kg/d X 2W)
HCQ (2 mg/kg/d X 4W)
2W POST TREATMENT
4W POST TREATMENT

FIG. 9A

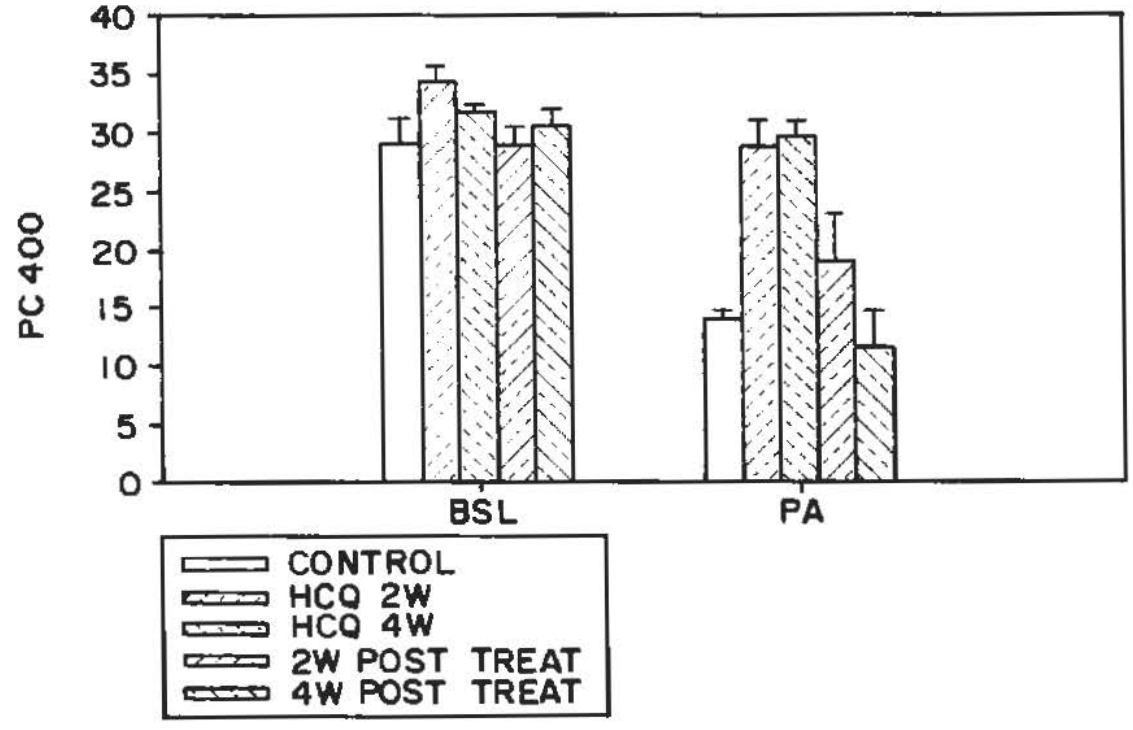

PC 400
40
35
30
25
20
15
10
5
0
BSL
PA
CONTROL
HCQ 2W
HCQ 4W
2W POST TREAT
4W POST TREAT

FIG. 9B

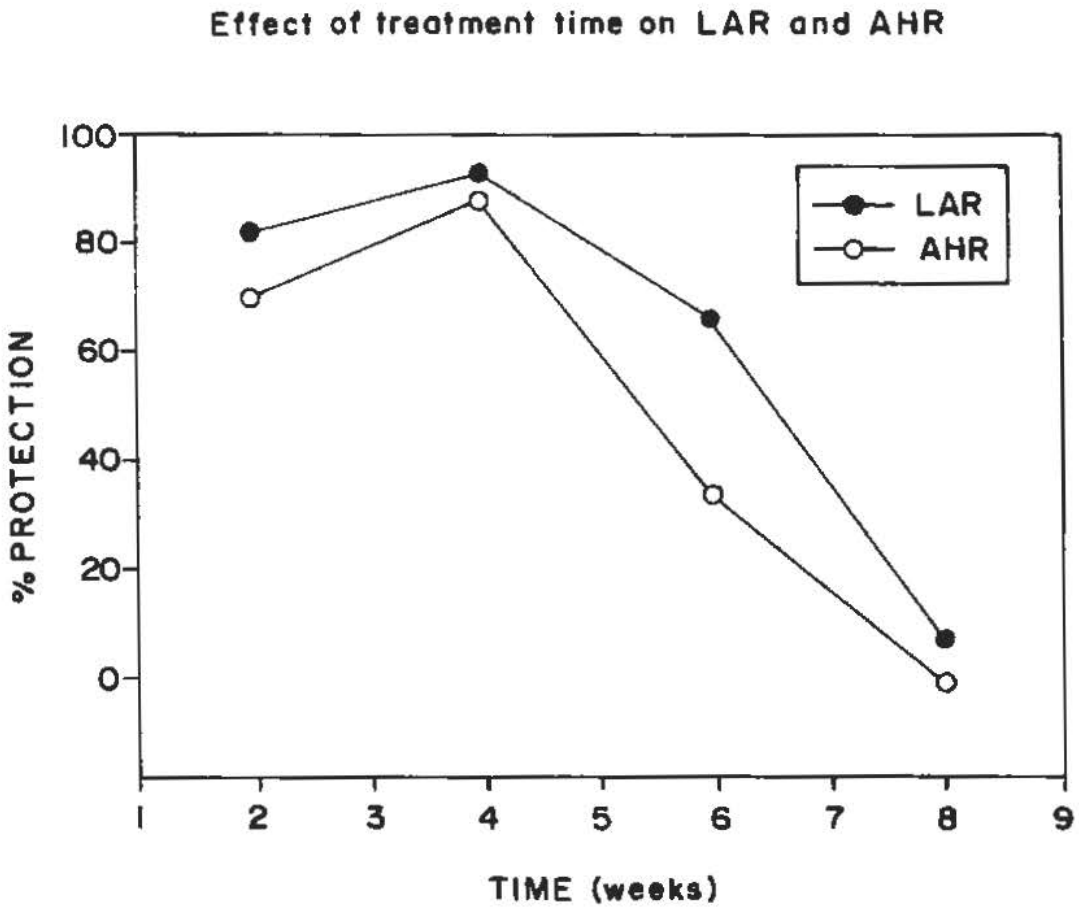

Effect of treatment time on LAR and AHR
100
80
60
40
20
0
% PROTECTION
LAR
AHR
1
2
3
4
5
6
7
8
9
TIME (weeks)

FIG.10

USES FOR ANTI-MALARIAL THERAPEUTIC AGENTS

RELATED APPLICATION

The present application claims benefit of U.S. patent application Ser. No. 60/132,008 filed on Apr. 30, 1999.

FIELD OF THE INVENTION

The present invention relates to a method for treating inflammatory conditions including pulmonary diseases states, such as asthma using anti-malarial agents via non-systemic administration.

BACKGROUND OF THE INVENTION

Inflammation is a phenomenon encountered in a variety of situations, including infections, transplantations, autoimmune disorders and following injury. There exists an immense range of distinct inflammatory reactions, each of which utilizes various immune mechanisms, such as memory T-cell and B-cells; cytokines and interleukins; preformed and synthesized chemical mediators, such as histamine, prostaglandins and leukotrienes; antibodies of different classes, as well as a whole host of disparate effector cells (e.g., killer cells, macrophages, neutrophils, basophils, eosinophils and the like).

Inflammatory diseases are among the most common maladies today. For example, asthma, a chronic inflammatory disorder of the airways, affects approximately 6–7% of the population of the U.S. (an estimated 17 million, according to a 1998 CDC forecast) and similar figures have been reported in other countries.

Asthma is a lung disease with the following characteristics: (1) airway obstruction that is reversible (but not completely so in some patients) either spontaneously or with treatment; (2) airway inflammation and (3) increased responsiveness to a variety of stimuli.

Airway inflammation contributes to the airway hyperresponsiveness, airflow limitation, respiratory symptoms and disease chronicity, which are characteristic of asthma (see Guidelines For The Diagnosis And Management of Asthma, Expert Panel Report 2, April 1997, NHLBI, NIH, Publication No. 97-4051, p.1). Asthma results from complex multi-cellular interactions among inflammatory cells, mediators, and other cells and tissues resident in the airway. Chronic inflammation of the airways is also a major cause of bronchial constriction, bronchial epithelial edema and mucus secretory abnormalities. Persistent airway inflammation is thought to lead to sub-basement membrane fibrosis which may cause permanent airway remodeling and chronic irreversible airway obstruction.

For these reasons, recent recommendations for asthma therapy have centered on the use of anti-inflammatory therapy. Anti-inflammatory therapy is designed to reduce the number of activated inflammatory cells, such as neutrophils, eosinophils, mast cells and lymphocytes and mediators such as cytokines and chemokines in airway tissues or secretions. Therapeutics that have been used in the treatment of airway inflammation include: glucocorticosteroids, cromones, theophylline and leukotriene modifiers (Inflammation in asthma: the cornerstone of the disease and target of therapy, W W. Busse, 1998, *J. Allergy Clin. Immunol.* 102, S17–S22.).

Human glucocorticoid hormones of the adrenal cortex and their synthetic analogues have been the most widely adopted class of therapeutic agents used to treat a wide range of inflammatory conditions such as rheumatoid arthritis, lupus, inflammatory bowel disease, and asthma. These agents act via specific glucocorticoid membrane receptors found on a wide variety of cells, including those mediating inflammation. Once bound to the cell, their effects are mediated by a well-defined sequences of steps (see Glucocorticosteroids, R P Schleimer, p. 638–660 in Allergy, Principles and Practice ed. E. Middleton, Mosby, St. Louis, 1998) which culminates in the association of the glucocorticoid-receptor complex with cellular nuclear chromatin with the subsequent suppression of inflammatory genes as well as other effects. These actions are manifest on both developing and mature cells. This allows the use of glucocorticoid agents in both systemic and topical forms, including oral, intravenous, depot intramuscular, ophthalmic drops, cutaneous ointment and cream, suppository, retention enema, nasal spray, and by inhalation.

Despite their short-term effectiveness, however, glucocorticoids have significant long-term shortcomings. Glucocorticoids do not appear to alter the underlying pathologic processes, and discontinuance is generally followed by increasing symptoms and evidence for renewed airway inflammation (Juniper 1991, *J. Allerg. Clin. Immunol.*, 87:483; *Waalkens Am. Rev. Resp. Dis.* 1993, 148:1252–57). Moreover, oral systemic corticosteroid treatment is complicated by multiple severe toxicities, including adrenal suppression, osteoporosis, cataract formation, glucose intolerance, obesity and hypertension.

Use of topical or organ-system directed delivery glucocorticosteroid hormones reduces but does not completely avoid all toxicity. For instance, even with inhaled glucocorticosteroids, there is a documented increased rate of cataract formation and growth retardation in children which is dose dependent. Furthermore, in many patients with more severe asthma, inhaled glucocorticosteroids appear to have efficacy only at elevated doses where significant systemic levels may appear via pulmonary absorption.

As a consequence of these shortcomings of glucocorticosteroids, a wide range of anti-inflammatory pharmaceuticals agents has been developed and proven effective for the treatment of a wide range of inflammatory diseases. These include anti-proliferative agents such as methotrexate which is used for treating rheumatoid arthritis and systemic lupus erythematosus and 6-mercapto purine analognes used for treating inflammatory bowel disease; alkylating agents such as cyclophosphamide used for treating systemic vasculitis; long-acting immunosuppressive or immunomodulating agents such as cyclosporine which is used for treating transplant rejection and sarcoidosis; gold salts used for treating rheumatoid arthritis, dapsone used for treating urticaria and cutaneous vasculitis; colchicine used for treating vasculitis and gout; and hydroxychloroquine (HCQ) used as a systemic anti-malarial agent for treating rheumatoid arthritis, systemic lupus erythematosus, and primary Sjögren's syndrome. (Bell 1983, *Am. J. Medicine*, 75:46–51; Rothfield 1984, *Am. J. Med.*, 85:53–56; Fox 1984, *Am. J. Med.*, 85:62–67).

According to conventional usage, each and every one of these agents except HCQ has been administered systemically via oral or parenteral dosing only. HCQ has only been administered heretofore by oral dosing. Conversely, none has been dosed via a local, targeted administration, such as inhalational delivery, for several reasons. First, a large majority of these agents exert their effects on developing cells found in the marrow and spleen. Local, targeted administration cannot reach nor affect such cells; only with systemic administration can tissue levels sufficient to affect these cellular reservoirs be achieved. Second, unlike gluco-

corticosteroid hormones, a majority of these agents have little effect on mature inflammatory cells. Thus, local, targeted administration is not viewed as conveying any significant advantage in terms of therapeutic effect. Lastly, end organ toxicity resulting from exposure to these agents may be appreciable and even life-threatening. Inasmuch as some of this toxicity is expressed by mucosal or serosal epithelial surfaces (e.g., stomatitis due to methotrexate and gold salts; gastrointestinal toxicity due to colchicine; bladder carcinoma due to cyclophosphamide), local, targeted administration of such agents has been viewed as unjustified in terms of presumed increased risk and the lack of a known advantage associated with direct application.

As a consequence, trials using gold salts, dapsone, methotrexate, cyclosporine and hydroxychloroquine (HCQ) as well as other anti-inflammatory treatments of asthma have uniformly relied on oral dosing (see Bernstein, *J. Allerg. Clin.*, 1996, 98:317-24; Berlow, *J. Allerg. Clin. Immunol.*, 1991, 87:710–15; Mullarkey NEJM 988, 38 (10):603–607; Alexander, *Lancet*, 1992, 339:324–328; Charous, 1990, *Ann. Allergy*, 68:80). Even newer pharmaceutical agents such as leukotriene receptor antagonists (zafirlukast and montelukast) and monoclonal anti-IgE antibodies are systemically administered due to lack of efficacy of local, targeted administration.

Only the anti-inflammatory pharmaceuticals nedocromil and cromolyn sodium are administered as local, targeted agents (via inhalation) due to the fact that these agents are only poorly absorbed by the gastrointestinal tract after oral dosing. These agents are seen as having only "mild to moderate" activity as asthma therapeutics (see Guidelines for the Diagnosis and Management of Asthma, Expert Panel Report 2, April 1997, NHLBI, NIH, Publication No. 97-4051, p. 32).

Among the quinoline antimalarials (e.g., quinine, chloroquine, amodiaquine, primaquine and mefloquine) there are certain compounds which are used as anti-inflammatory therapeutics (Antimalarial pharmacokinetics and treatment regimens, N J White (1992) *Br. J. Clin. Pharmac.*, 34, 1–10). The 4-aminoquinoline class of antimalarial compounds, in particular chloroquine and hydroxychloroquine have been used as anti-inflammatory and immunomodulatory agents in the treatment of rheumatoid arthritis and systemic lupus erthematosus for the past 20 years. These compounds increase pH within intracellular vacuoles and alter processes such as protein degradation by acidic hydrolases, lipid mobilization and antigenic processing (Mechanism of Action of Hydroxychloroquine as an Antirheumatic Drug, R I Fox (1993) Seminars in Arthritis and Rheumatism, 23, Suppl. 1, 82–91). Although these drugs have been known for several years, they have been administered heretofore orally for specifically treating anti-inflammatory conditions.

Recently, U.S. Pat. No. 4,181,725 to Voorhees, et al. discloses the use of various drugs, such as chloroquine and hydroxychloroquine, for the treatment of skin proliferative diseases, such as psoriasis.

However, until now, no one has suggested administering these drugs locally for treating anti-inflammatory conditions which are not on the surface of the skin.

For example, as a systemically delivered immunomodulatory agent, hydroxychloroquine (HCQ) in particular has been demonstrated to have multiple anti-inflammatory effects and has been shown to have significant advantages in safety over the other available systemic anti-inflammatory agents mentioned above. For this reason, HCQ is the only systemic anti-inflammatory that has been approved, by both the FDA's Pulmonary Branch and an independent Investigational Review Board, for use in a double-blind trial in non-oral glucocorticosteroid-dependent asthmatic subjects (Hydroxychloroquine improves airflow and lowers circulating IgE levels in subjects with moderate symptomatic asthma, B. L. Charous, E. F. Halpern, G. C. Steven (1998), *J. Allergy Clin. Immunol.*, 102, 198–203).

The current delivery methods for HCQ, such as oral administration, have several drawbacks, however. When delivered orally, the rate of onset is slow, and the agent actively concentrates in organs other than the target organ. As a consequence, a relatively high dosage and long term treatment required. In addition to added cost and low efficiency such a high-dosage, long-term treatment carries a risk, however slight, of ocular toxicity. (Antimalarial ocular toxicity, a critical appraisal, D. A. Albert, L. K. L. Debois, K. F. Lu (1998) J. of Clin. Rheumatol. (US) 4, 57–62.)

Despite the drawbacks, the anti-malarials, such as HCQ, have only been administered systemically, e.g., orally for treating anti-inflammatory conditions, such as asthma, and topically on the surface of the skin for treating dermatological diseases, such as proliferative skin diseases. No one heretofore even suggested that they be administered by other means for treating anti-inflammatory conditions, especially since a change in the mode of administration may substantially alter drug action.

The choice of drug delivery methods requires full appreciation of the pharmacologic activities of the agent including tissue distribution, metabolism and cellular effects as well as an understanding of the interaction of the drug with the specific underlying pathological processes of the disease under treatment. Proof of efficacy by one route of administration does not imply the presence of a desired drug effect when administered via an alternate route of administration. For example, see, Fahy, et al. in *Am. J. Respir. Crit. Care Med.*, 1999, 160:1023–1027 which showed that intravenous administration of Anti IgE(E25) was effective for treating allergic asthma, but that a different route of administration, viz., inhalation, was virtually ineffective in treating allergic asthma. Moreover, a change in drug administration from systemic to methods designed to target drug delivery to affected tissues may substantially increase drug effects in selective tissue, but carries the risk of increased local toxicity. It may promote salutary effects such as decreasing the time to onset of action, but may result in loss of overall efficacy due to the restricted nature of tissue distribution.

Because the route of drug administration determines bioavailability and tissue levels and distribution, change in delivery may modify fundamentally the location, nature, extent and duration of anti-inflammatory actions, as well as alter dosing requirements and toxicities. As the skilled artisan is well aware, there can be no assumption that if a drug works when administered one way, it will work when administered another way, particularly when drugs are delivered to mucosal and serosal tissues. In effect, any change in administration method may cause undesired effects.

However, the present inventor has shown that when anti-malarials exhibiting anti-inflammatory activity are administered locally to a patient in need of treatment, the anti-malarials agents were unexpectedly more efficacious in treating inflammatory conditions than when administered systemically.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a novel method for the administration of an anti-malarial

agent that will reach the diseased area of the patient rapidly. Specifically, the present invention provides a method for treating an inflammatory condition, especially in the pulmonary system, comprising administering via localized delivery to an area of inflammation in a subject in need thereof, an anti-inflammatory effective amount of an anti-malarial compound thereto. An example of a particular application of the method of the invention is treatment of pulmonary inflammatory conditions, such as asthma, by inhalation of an aerosolized anti-malarial compound. The method of the invention unexpectedly shows a rapid, therapeutic effect compared to systemic administration.

It is another object of the present invention to provide for a kit comprising a pharmaceutical composition comprising an anti-malarial compound in effective amounts and a pharmaceutical carrier thereof, in combination with a inhaler or other device through which the preparation can be delivered in a targeted and localized manner, such as would occur by inhalation of an aerosolized preparation.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an x-y plot of % change of SR_l (specific lung resistance) from baseline over time. FIG. **1** shows the difference in SR_l between HCQ treated sheep and historical controls immediately after antigen challenge.

FIG. **2** is an x-y plot of % change of SR_l (specific lung resistance) from baseline over time. FIG. **2** shows the difference in late phase asthmatic reaction between HCQ treated sheep and historical controls.

FIG. **3** is a bar graph showing the baseline and post-antigen challenge differences in carbachol reactivity (PC_{400} as measured in breath units) between HCQ treated sheep and historical controls.

FIG. **4A** graphically represents a time course of antigen-induced changes in specific lung resistance (SR_l) in three sheep treated with aerosol HCQ, twice a day. Responses are compared to the animals' historical control (Control 1) and a two week follow-up control (Control 2).

FIG. **4B** graphically show the effect of HCQ on airway responsiveness. BSL baseline PA is 24 h post antigen. A decrease in the PC_{400} indicates the development of airway hyperresponsiveness. Values are mean±se for 3 sheep. Statistical analysis is found in Table 3.

FIG. **5A** graphically shows a time course of antigen-induced changes in specific lung resistance (SR_l) in three sheep treated with oral HCQ, twice a day. Responses are compared to the animals' historical control (Control 1) and a two week follow-up control (Control 2).

FIG. **5B** graphically shows the effect of HCQ on airway responsiveness. BSL=baseline, PA=24 h post antigen. A decrease in the PC_{400} indicates the development of airway hyperresponsiveness. Values are mean±se for 3 sheep. Statistical analysis is found in Table 3.

FIG. **6A** graphically shows the time course of antigen-induced changes in specific lung resistance (SR_l) in three sheep treated with aerosol HCQ, once a day. Responses are compared to the animals' historical control (Control 1) and a two week follow-up control (Control 2).

FIG. **6B** graphically demonstrates the effect of HCQ on airway responsiveness. BSL baseline PA=24 h post antigen. A decrease in the PC_{400} indicates the development of airway hyperresponsiveness. Values are mean±se for 3 sheep. Statistical analysis is found in Table 3.

FIG. **7A** graphically shows the time course of antigen-induced changes in specific lung resistance (SR_l) in three sheep treated with differing doses of aerosol HCQ, once a day.

FIG. **7B** demonstrates graphically the effect of HCQ on airway responsiveness. BSL baseline PA=24 h post antigen. A decrease in the PC_{400} indicates the development of airway hyperresponsiveness. Values are mean±se for 3 sheep. Statistical analysis is found in Table 3.

FIG. **8** graphically shows the mean percent (%) protection of late airway response (LAR) and airway hyperresponsiveness (AHR) with differing doses of aerosol HCQ. Values are mean for 3 sheep.

FIG. **9A** graphically shows the time course of antigen-induced changes in specific lung resistance (SR_l) in three sheep treated with aerosol HCQ, once daily for 4 weeks. Responses are compared to the animals' historical control (Control) and follow-ups 2 and 4 weeks after stopping drug treatment.

FIG. **9B** shows graphically the effect of HCQ on airway responsiveness. BSL baseline PA=24 h post antigen. A decrease in the PC_{400} indicates the development of airway hyperresponsiveness. Values are mean±se for 3 sheep. Statistical analysis is found in Table 3.

FIG. **10** graphically demonstrates the mean percent (%) protection of late airway response (LAR) and airway hyperresponsiveness (AHR) over time. Values are mean for 3 sheep.

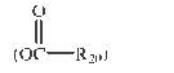
DETAILED DESCRIPTION OF THE INVENTION

The present inventor has discovered that an anti-malarial agent administered in a local or targeted fashion, directly to the diseased organ or area of inflammation of a patient, is much more effective and efficacious than when administered orally with the result that the agent reaches a therapeutic level with surprising rapidity, in the targeted tissue or organ, while undesirable side effects are minimized. Accordingly, the present invention relates generally to the treatment of inflammatory conditions or disease states by local administration of an anti-inflammatory effective amount of an anti-malarial agent. By anti-malarial, as used herein, it is meant that the drug has been historically belonged to the class of drugs known as anti-malarials. Preferred antimalarials include aminoquinolines especially 8- and 4-aminoquinolines, acridines, e.g., 9-amino acridines and quinoline methanols, e.g., 4-quinolinemethanols.

Compounds used in the Invention

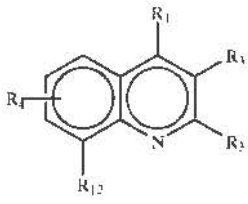
Compounds suitable for the present invention are anti-malarial agents that have immunomodulatory and anti-inflammatory effects. Anti-malarial agents are well known in the art. Examples of anti-malarial agents can be found, for example, in GOODMAN AND GILMAN'S; THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, chapters 45–47, pages 1029–65 (MacMillan Publishing Co. 1985), hereby incorporated by reference.

The preferred anti-malarial compounds are quinine based or are aminoquinolines, especially 4- and 8-amino quinolines. An especially preferred class of antimalarials has a core quinoline structure (examples are mefloquine and quinine) which is usually substituted at one or more positions, typically at least at the 4- and/or 8-positions. One skilled in the art would understand that such agents could be administered in derivatized forms, such as pharmaceutically acceptable salts, or in a form that improves their pharmacodynamic profiles, such as esterification of acid or alcohol substituents with lower alkyls (e.g., C_{1-6}) or lower alkanoyloxy



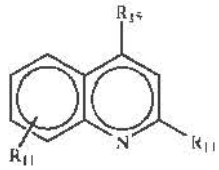
respectively, wherein R_{30} is lower alkyl. Another class of antimalarials, exemplified by quinacrine, is based on an acridine ring structure, and may be substituted in the manner described above.

Especially preferred compounds for use in the present invention are aminoquinolines, including 4-amino and 8-aminoquinolines and their derivatives (collectively, "aminoquinoline derivatives") and aminoacridines, especially 9-amino acridines. The preferred 4- and 8 aminoquinolines and 9-amino acridines are described by the following formula:



or

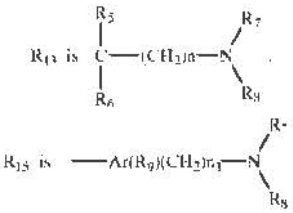
VII



or pharmaceutically acceptable salts thereof, wherein

R_2 and R_3 are independently hydrogen, or lower alkyl or R_2 and R_3 taken together with the carbon atoms to which they are attached form an aryl ring, which ring may be unsubstituted or substituted with an electron withdrawing group or an electron donating group,

one of R_1 and R_{12} is NHR_{13} while the other is hydrogen;



R_4, R_{12}, R_{13} and R_{14} are independently hydrogen or an electron donating group or electron withdrawing group;

R_5 and R_6, are independently hydrogen or lower alkyl which may be unsubstituted or substituted with an electron withdrawing or electron donating group;

R_7 and R_8 are independently hydrogen or lower alkyl, which may be unsubstituted or substituted with an electron withdrawing or electron donating group;

Ar is aryl having 6–18 ring carbon atoms;

R_9 is hydrogen or hydroxy or lower alkoxy or

R_{25} is lower alkyl or hydrogen; and

n and n_1 are independently 1–6.

As used herein, the terms "electron donating groups" and "electron withdrawing groups" refer to the ability of a substituent to donate or withdraw an electron relative to that of hydrogen if the hydrogen atom occupied the same position in the molecule. These terms are well understood by one skilled in the art and are discussed in Advanced Organic Chemistry, by J. March, John Wiley & Sons, New York, N.Y., pp. 16–18 (1985) and the discussion therein is incorporated herein by reference. Electron withdrawing groups include halo, including bromo, fluoro, chloro, iodo and the like; nitro; carboxy; carbalkoxy; lower alkenyl; lower alkynyl; formyl; carboamido; aryl; quaternary ammonium compounds, and the like. Electron donating groups include such groups as hydroxy; lower alkoxy; including methoxy, ethoxy and the like; lower alkyl, such as methyl; ethyl, and the like.; amino; lower alkylamino; diloweralkylamino; aryloxy, such as phenoxy and the like; arylalkoxy, such as benzyl and the like; mercapto, alkylthio, and the like. One skilled in the art will appreciate that the aforesaid substituent may have electron donating or electron withdrawing properties under different chemical conditions.

The term alkyl, when used alone or in conjunction with other groups, refers to an alkyl group containing one to six carbon atoms. It may be straight-chained or branched. Examples include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, pentyl, neopentyl, hexyl and the like.

Lower alkoxy refers to an alkyl group which is attached to the main chain by an oxygen bridging atom. Examples include methoxy, ethoxy, and the like.

Lower alkenyl is an alkenyl group containing from 2 to 6 carbon atoms and at least one double bond. These groups may be straight chained or branched and may be in the Z or E form. Such groups include vinyl, propenyl, 1-butenyl, isobutenyl, 2-butenyl, 1-pentenyl, (Z)-2-pentenyl, (E)-2-pentyl, (Z)-4-methyl-2-pentenyl, (E)-4-methyl-2-pentenyl, allyl, pentadienyl, e.g., 1,3 or 2,4-pentadienyl, and the like. It is preferred that the alkenyl group contains at most two carbon-carbon double bonds; and most preferably one carbon-carbon double bond.

The term alkynyl include alkynyls containing 2 to 6 carbon atoms. They may be straight chain as well as branched. It includes such groups as ethynyl, propynyl, 1-bntynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-pentynyl, 3-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, and the like.

The term aryl refers to an aromatic group containing only carbon ring atoms which contains up to 18 ring carbon atoms and up to a total of 25 carbon atoms and includes the polynuclear aromatic rings. These aryl groups may be monocyclic, bicyclic, tricyclic, or polycyclic, and contain fused rings. The group includes phenyl, naphthyl, anthracenyl, phenanthranyl, xylyl, tolyl and the like.

The aryl lower alkyl groups include, for example, benzyl, phenethyl, phenpropyl, phenisopropyl, phenbutyl, diphenylmethyl, 1,1-diphenylethyl, 1,2-diphenylethyl and the like.

The term halo include fluoro, chloro, bromo, iodo and the like.

The preferred values of R_2 and R_3 are independently hydrogen or alkyl containing 1–3 carbon atoms. It is most preferred that R_3 is hydrogen. It is most preferred that R_2 is hydrogen or alkyl containing 1–3 carbon atoms, especially methyl or ethyl. It is most preferred that R_2 is hydrogen or alkyl containing 1–3 carbon atoms or hydrogen and R_3 is hydrogen.

Alternatively, if R_2 and R_3 are taken together with the carbon atoms to which they are attached, it is most preferred that they form a phenyl ring. The phenyl ring is preferably unsubstituted or substituted with lower alkoxy, hydroxy, lower alkyl or halo.

It is preferred that R_4 is an electron withdrawing group, more specifically, halo, especially chloro, or is hydroxy or lower alkoxy. It is even more preferred that when R_1 is NHR_{13}, R_4 is substituted on the 7-position of the quinoline ring. It is most preferred that when R_1 is NHR_{13}, R_4 is halo.

However, when R_{12} is NHR_{13}, it is preferred that R_4 is an electron donating group, such as hydroxy or alkoxy. More specifically, it is preferred that R_4 is methoxy or ethoxy when R_{12} is NHR_{13}. It is even more preferred that R_4 is on the 6-position of the quinoline ring when R_{12} is NHR_{13}.

It is preferred that one of R_5 and R_6 is hydrogen and the other is lower alkyl. It is even more preferred that R_5 is hydrogen and R_6 is lower alkyl, especially alkyl containing 1–3 carbon atoms and most preferably methyl.

The preferred value of R_7 is lower alkyl, especially alkyl containing 1–3 carbon atoms and most preferably methyl and ethyl.

Preferred values of R_8 is lower alkyl containing 1–3 carbon atoms, and most preferably methyl and ethyl. However, it is preferred that the alkyl group is unsubstituted or if substituted, is substituted on the omega (last) carbon in the alkyl substituent. The preferred substituent is lower alkoxy and especially hydroxy.

The preferred R_9 is lower alkoxy and especially hydroxy.

R_{11} is preferably an electron withdrawing group, especially trifluoromethyl. It is preferably located on the 8-position of the quinoline ring.

R_{14} is preferably an electron withdrawing group, and more preferably trifluoromethyl. It is preferably present on the 2-position of the quinoline ring.

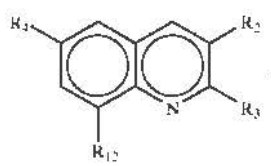
It is preferred that R_{15} is

wherein R_7 and R_8 are independently alkyl containing 1–3 carbon atoms and Ar is phenyl.

In both R_{13} and R_{15}, it is preferred that R_7 and R_8 contain the same number of carbon atoms, although one may be unsubstituted while the other is substituted. It is also preferred that R_7 and R_8 are the same.

The preferred value of n is 3 or 4 while the preferred value of n_1 is 1.

Preferred anti-malarials have the structure:



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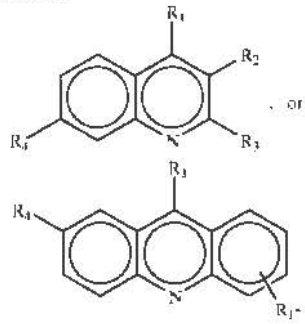
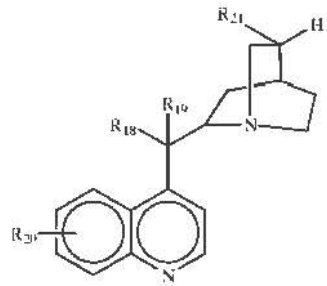


wherein R_{12}, R_4, R_2, R_3 and R_1 are as defined hereinabove and R_{17} is hydrogen, halo, lower alkyl, lower alkoxy.

Preferred antimalarials include the 8-aminoquinolines, 9-aminocridines and the 7-chloro-4-aminoquinolines. Examples include pamaquine, primaquine, pentaquine, isopentaquine, quinacrine salts, 7-chloro-4-aminoquinolines, such as the chloroquines, hydroxychloroquines, sontoquine, amodiaquine and the like.

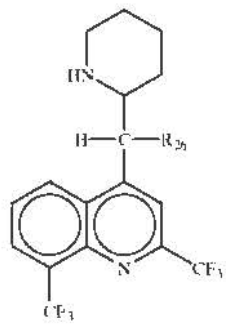
Another class of preferred antimalarial are cinchono alkaloids and 4-quinoline methanols, such as those having the formula:



wherein one of R_{18} and R_{19} is hydroxy or loweralkylcarbonyloxy or hydrogen, and the other is H, and R_{20} is hydrogen or loweralkoxy and R_{21} is hydrogen or $CH{=}CH_2$.

Examples include rubane, quinine, quinidine, cinchoidine, epiquinine, epiquinidine, cinchonine, and the like.

Another preferred quinoline methanol is mefloquine or derivative thereof of the formula:



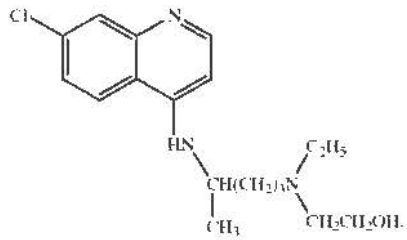
wherein R_{27} is lower alkoxy,

and especially hydroxy and

R_{27} is lower alkyl.

The most preferred anti-malarials include mefloquinine, and chloroquine and its congeners, such as hydroxychloroquine (HCQ), amodiaquine, pamaquine and pentaquine and pharmaceutically acceptable salts thereof.

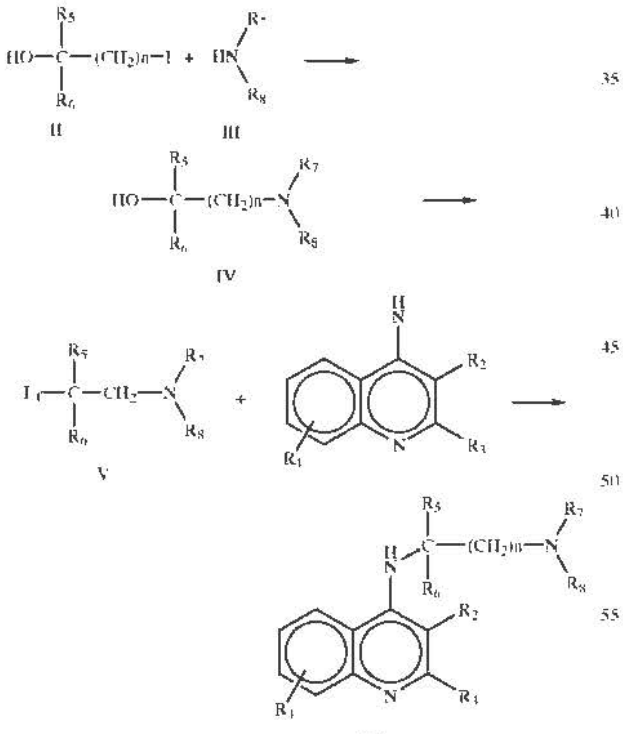
The most preferred anti-malarial agent for the invention is hydroxychloroqnine, shown below, or a pharmaceutically suitable salt thereof, such as hydroxychloroquine sulfate



hydroxychloroquine

The antimalarials are commercially available or are prepared by art recognized techniques known in the art.

For example, the 4-aminoquinolines can be prepared as follows:



II III

IV

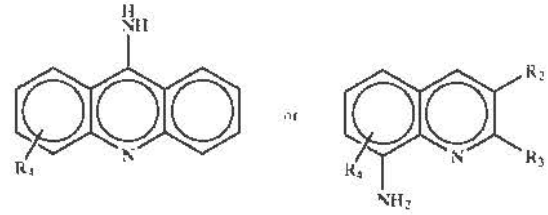
V

VI

In the above scheme, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, and n are as defined hereinabove, and I and L_1 are good leaving groups, such as halides or sulfonates, e.g., mesylates or aryl sulfonates, e.g., tosylates, brosylates, and the like.

The compound of Formula II containing a leaving group, I, is reacted with the amine of Formula III under amine alkylation conditions. The alcohol group in the product of Formula IV (OH group) is converted to a leaving group by reactions known in the art. For example, sulfonic esters, such as tosylates, mesylates or brosylates are prepared by treatment of sulfonic halides of the formula $R_{23}SO_2X_1$ wherein X_1 is halide and R_{23} is lower alkyl, such as methyl, aryl or substituted aryl, such as p-bromophenyl, p-tolyl with the alcohol of Compound IV. The reaction is usually effected in the presence of a weak base, such as pyridine. Alternatively, the alcohol can be converted to the corresponding halide by reaction of the alcohol of IV with HCl, HBr, thienyl chloride, PCl_3, PCl_5 or $POCl_3$. The product of V is then reacted under amine alkylation conditions with the quinoline amine to provide the 4-amino quinoline product.

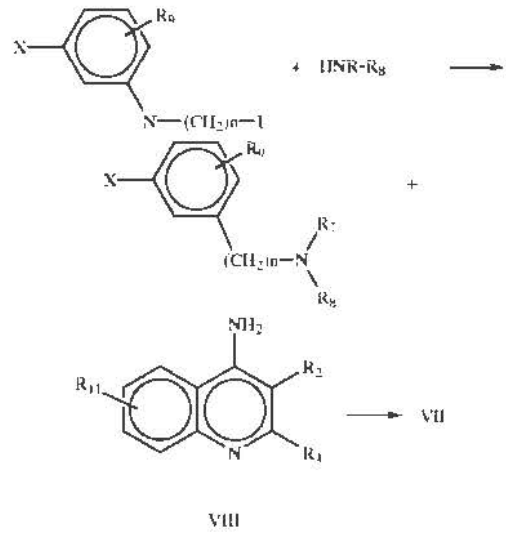
The 9-aminoacridines and the 8-aminoquinoline are prepared similarly. More specifically, the product of V is reacted with



under amine alkylation reaction conditions.

The reactions described hereinabove are preferably conducted in solvents which are inert to the reactants and products and in which the reactants, are soluble, such as tetrahydrofuran, ethers, acetones, and the like. It is preferred that the solvents are volatile. The reactions are conducted at effective reaction conditions and are conducted at temperatures ranging from room temperature up to and including the reflux temperatures of the solvent.

An exemplary procedure for the preparation of compounds of Formula VII is as follows:



VIII

The first reaction is a simple amino alkylation reaction as described hereinabove. The product thereof is reacted with the amine of Formula III in the presence of a strong base such as amide to form the product of Formula VII.

Many of the compounds described hereinabove, especially the 4-quinoline methanols, can be converted to ethers by reacting the salt of the alcohols with an alkyl halide or

arylalkyl halide or aryl halide to form the corresponding ether. Moreover, the esters can be formed from the hydroxy group by reacting the alcohol, such as the 4-quinoline methanol, with an alkanoic acid, arylalkonic acid or aryloic acid or acylating derivatives thereof in the presence of acid, for example, HCl, H_2SO_4 or p-toluene sulfonic acid under esterification conditions.

If any of the groups on R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 are reactive with any of the reagents used or with any of the reactants or products, then they would be protected by protecting groups known in the art to avoid unwanted side reactions. This protecting groups normally used in synthetic organic chemistry are well known in the art. Examples are found in PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, by T. W. Greene, John Wiley & Sons, Inc., NY 1981 ("Greene"), the contents of which are incorporated by reference.

Therapeutical Compositions of the Invention

A therapeutic composition within the present invention is formulated for localized (targeted) delivery and includes at least one anti-malarial agent, as described above. As previously emphasized, the present invention contemplates administration of the anti-malarial compounds to internal organs, such as the lungs, or the eye, or internal muscles or tissues, by local or targeted delivery. "Local or topical delivery" and "locally administering" are used in this description to denote direct delivery to the site, such that the therapeutic agent acts directly on affected tissue or the area of a diseased organ. Local delivery contrasts with methods by which a therapeutic agent is administered orally, or otherwise systemically, and is absorbed into the circulation for distribution throughout the patient's body. Examples of local delivery include inhalation, nasal spray, suppository, and eye drops and by injections directly to the organ, muscle or tissue. It is to be noted that the anti-malarial compound is not injected intravenously, that is, into the circulatory blood of the patient. Topical delivery to the skin, however, is not contemplated in the practice of "local or topical delivery" as defined above. These compositions may be solutions, suspensions and admixtures, for example. As one having ordinary skill in the art would understand, they may be prepared essentially as detailed in REMINGTON'S PHARMACEUTICAL SCIENCES, 18th ed., (Mack Publishing Co. 1990) ("Remingtons"), which is hereby incorporated by reference.

The compounds of the present invention are present in the pharmaceutical compositions in anti-inflammatory effective amounts. The anti-malarial compounds used in the present invention are administered in an amount which depends upon the condition of the subject, the type of inflammatory condition of which the subject suffers, the timing of the administration of the subject, the route of administration, the particular formulation and the like. However, unlike oral dosing which takes usually about a month before there is a noticeable or measurable onset of action, onset of action of the area of inflammation, from local administration of the anti-malarials is noticed or observed within 10 days after initial administration. Effective amounts of the anti-malarial compounds, hereinafter known as drug, is that amount which provides the observable onset of action within 10 days, and more preferably within 7 days after administration. Significantly less amount of drug is given locally than by systemic administration to achieve efficacious results, and the onset of action, as indicated hereinabove, is much faster by local administration. It is preferred that the drug is administered locally at a dosage of about 0.020 to about 2 mg/kg animal weight and more preferably from about 0.100 to about 1 mg/kg and most preferably from about 0.200 to about 0.650 mg/kg.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system.

Solid or liquid particulate forms of the active compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. In general, particles ranging from about 1 to 10 microns in size are within the respirable range. The therapeutic composition containing the anti-malarial compounds are preferably administered by direct inhalation into the respiratory system for delivery as a mist or other aerosol or dry powder. Particles of non-respirable size which are included in the aerosol tend to be deposited in the throat and swallowed; thus the quantity of non-respirable particles in the aerosol is preferably minimized.

The dosage of active compound via this route will vary depending on the condition being treated and the state of the subject, but generally may be an amount sufficient to achieve dissolved concentrations of anti-malarial compound on the airway surfaces of the subject. Depending upon the solubility of the particular formulation of active compound administered, the daily dose may be divided among one or several unit dose administrations. The daily dose by weight will depend upon the age and condition of the subject. Such a daily dose of the anti-malarial compound ranges from about 0.20 mg/kg per day to about as 2.0 mg per day, and more preferably from about 0.1 to about 1 mg/kg and most preferably from about 0.200 mg/kg to about 0.650 mg/kg. In the most preferred embodiments, only one dose is administered to the patient per day. The doses of the active compounds may be provided as one or several prepackaged units.

In the manufacture of a formulation according to the invention, the anti-malarial compounds or the pharmaceutically acceptable salts are typically admixed with, inter alia, an acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit dose formulation. One or more drugs may be incorporated in the formulations of the invention, which formulations may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixing the drug with the other various components described hereinbelow present therein.

Aerosols of liquid particles comprising the anti-malarial compounds may be produced by any suitable means, such as inhalatory delivery systems. One is a traditional nebulizer which works in a mechanism similar to the familiar perfume atomizer. The airborne particles are generated by a jet of air from either a compressor or compressed gas cylinder passing through the device (pressure driven aerosol nebulizer). In addition, newer forms utilize an ultrasonic nebulizer by vibrating the liquid at speed of up to about 1 MHz. See, e.g., U.S. Pat. No. 4,501,729, the contents of which are incorporated by reference. Nebulizers are commercially available devices which transform solutions or suspensions of the active ingredient into a therapeutic aerosol mist either by means of acceleration of compressed gas, typically air or oxygen, through a narrow venturi orifice or by means of ultrasonic agitation. Suitable formulations for use in nebu-

lizers consist of the active ingredient in a liquid carrier. The carrier is typically water (and most preferably sterile, pyrogen-free water) or a dilute aqueous alcoholic solution, preferably made isotonic but may be hypertonic with body fluids by the addition of, for example, sodium chloride. Optional additives include preservatives if the formulation is not made sterile, for example, methyl hydroxybenzoate, as well as antioxidants, flavoring agents, volatile oils, buffering agents and surfactants, which are normally used in the preparation of pharmaceutical compositions.

Aerosols of solid particles comprising the anti-malarial compound may likewise be produced with any solid particulate medicament aerosol generator. Aerosol generators for administering solid particulate medicaments to a subject produce particles which are respirable, as explained above, and generate a volume of aerosol containing a predetermined metered dose of a medicament at a rate suitable for human administration. One illustrative type of solid particulate aerosol generator is an insufflator. Suitable formulations for administration by insufflation include finely comminuted powders which may be delivered by means of an insufflator or taken into the nasal cavity in the manner of a snuff. In the insufflator, the powder (e.g., a metered dose thereof effective to carry out the treatments described herein) is contained in capsules or cartridges, typically made of gelatin or plastic, which are either pierced or opened in situ and the powder delivered by air drawn through the device upon inhalation or by means of a manually-operated pump. The powder employed in the insufflator consists either solely of the active ingredient or of a powder blend comprising the anti-malarial compound, a suitable powder diluent, such as lactose, and an optional surfactant. A second type of illustrative aerosol generator comprises a metered dose inhaler. Metered dose inhalers are pressurized aerosol dispensers, typically containing a suspension or solution formulation of the anti-malarial compound in a liquified propellant. During use these devices discharge the formulation through a valve, adapted to deliver a metered volume, from 10 to 22 microliters to produce a fine particle spray containing the anti-malarial compound. Suitable propellants include certain chlorofluorocarbon (compounds, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane and mixtures thereof. The formulation may additionally contain one or more co-solvents, for example, ethanol, surfactants, such as oleic acid or sorbitan trioleate, antioxidants and suitable flavoring agents.

Any propellant may be used in carrying out the present invention, including both chlorofluorocarbon-containing propellants and non-chlorofluorocarbon-containing propellants. Fluorocarbon aerosol propellants that may be employed in carrying out the present invention including fluorocarbon propellants in which all hydrogen are replaced with fluorine, chlorofluorocarbon propellants in which all hydrogens are replaced with chlorine and at least one fluorine, hydrogen-containing fluorocarbon propellants, and hydrogen-containing chlorofluorocarbon propellants. Examples of such propellants include, but are not limited to: CF_3CHFCF_2, $CF_3CH_2CF_2H$, CF_3CHFCF_3, $CF_3CH_2CF_3$, $CF_3CHCl—CF_2Cl$, $CF_3CHCl—CF_3$, $CF_3CHCl—CH_2Cl$, $CF_3CHF—CF_2Cl$, and the like. A stabilizer such as a fluoropolymer may optionally be included in formulations of fluorocarbon propellants, such as described in U.S. Pat. No. 5,376,359 to Johnson.

Compositions containing respirable dry particles of micronized anti-malarial compounds may be prepared by grinding the dry active compound, with e.g., a mortar and pestle or other appropriate grinding device, and then passing the micronized composition through a 400 mesh screen to break up or separate out large agglomerates.

The aerosol, whether formed from solid or liquid particles, may be produced by the aerosol generator at a rate of from about 10 to 150 liters per minute. Aerosols containing greater amounts of medicament may be administered more rapidly. Typically, each aerosol may be delivered to the patient for a period from about 30 seconds to about 20 minutes, with a delivery period of about 1 to 5 minutes being preferred.

The particulate composition comprising the anti-malarial compound may optionally contain a carrier which serves to facilitate the formation of an aerosol. A suitable carrier is lactose, which may be blended with the active compound in any suitable ratio.

For example, hydroxychloroquine sulfate is a colorless crystalline solid which is readily soluble in water. Inhaled liquid forms may be formulated to contain such additives as are typically used in such pharmaceutical preparations, including, but not limited to an acceptable excipient and/or surfactant. A therapeutic composition of HCQ may be preformulated in liquid form, or prepared for the addition of a suitable carrier, like sterile water or physiological saline, immediately prior to use. The aerosol containing HCQ typically contain a propellant especially a fluorocarbon propellant. See Remington's, chapter 92. A particularly useful composition of HCQ is formulated in a nebulizer, for the treatment of a variety of pulmonary conditions. For the preparation of HCQ in inhaled powder form, the compound is finely divided, or micronized to enhance effectiveness, and admixed with a suitable filler. Inhaled powders may contain a bulking agent and/or stabilizer, as described hereinabove. Id., chapter 88. An insufflator (powder blower) may be employed to administer the fine powder.

The antimalarial compounds may be administered by other methods of local delivery, as defined herein. Compositions for these other mode of local delivery may include sterile aqueous solutions which may also contain buffers, diluents and other suitable additives and may be administered in other forms, such as oral pastes or ointment, retention enemas, suppositories, and injectable solutions, which injectable solutions are administered directly to internal organs or tissues and not intravenously.

The anti-malarial compounds may, where appropriate, be conveniently present in discrete unit dosage forms and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active compound, i.e., the anti-malarial compound with liquid carriers, solid matrices, semi-solid carriers, finely divided solid carriers or combinations thereof, and then, if necessary, shaping the product into the desired delivery system. Methods for admixing a pharmaceutical with a carrier are known in the art and are applicable to the present formulation.

The anti-malarial compounds may also be formulated as an ophthalmic product, like liquid eye drops or an ophthalmic ointment or nose drops or spray. See Remington's, Chapter 86. Drops, such as eye drops or nose drops, may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilizing agents or suspending agents. Drops can be delivered via a simple eye dropper-capped bottle or eye-dropper, or via a plastic bottle adapted to deliver liquid contents dropwise, via a specially shaped closure. Ophthalmic preparations typically contain at least one compound in a sterile isotonic solution, for example, sodium chloride or boric acid. They may contain

agents that increase viscosity, like methylcellulose, polyvinyl alcohol or hydroxymethyl cellulose.

The compounds also may be formulated advantageously as nasal sprays, oral pastes, ointments to be administered directly to the organ, such as the eye, and retention enemas, and other means known to one of ordinary skill in the art for local delivery.

Drugs can be administered by the lower enteral route, i.e., through the anal portal into the rectum or lower intestine. Rectal suppositories, retention enemas or rectal catheters can be used for this purpose. The drug may be administered in unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by the admixture of the anti-malarial compounds with the softened or melted carriers followed by chilling and shaping into molds.

The pharmaceutical forms suitable for injectable use directly into muscle or tissue include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents, delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the anti-malarial compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required followed by filtered sterilization. Generally, dispersions are prepared by incorporating the sterilized anti-malarial compound into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the anti-malarial compound plus any additional desired ingredient from previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well-known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. More than one anti-malarial compound can also be incorporated into the pharmaceutical compositions.

It is especially advantageous to formulate local compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of anti-malarial compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the anti-malarial compound utilized and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an anti-malarial compound for the treatment of anti-inflammatory conditions in living subjects having a diseased condition in which bodily health is impaired as hereinbelow disclosed.

Therapeutic Rationale

The inventive methods, detailed below, may be applied by the clinician to treat a variety of inflammatory conditions. Inflammatory conditions typically involve activation of the immune system, usually via steps of antigen recognition and presentation and T-cell activation. Immune responses are promoted by chemotactic, proinflammatory mediators including leukotrienes, and cytokines and interleukins such as IL-1, Il-4 or TNF as well as effector cells such as neutrophils, macrophages or eosinophils. Antibodies, including allergic IgE class antibodies, may also participate which in turn may elicit mast cell activation and triggering responses. Granulomatous inflammation resulting from cell-mediated responses characterizes some inflammatory disease states. The anti-inflammatory agents of the present invention retard the progression of these biochemical processes described hereinabove.

Although the inventor does not wish to be bound by any theory of mechanism of the invention, it is believed that the therapeutic approach of the present invention effectively inhibits or attenuates at least one of the inflammation-related processes. The inhibition or attenuation of one or more of the underlying causative or exacerbating processes is effected by the anti-malarial agents that have anti-inflammatory effect, thus results in an effective-treatment of a variety of inflammatory conditions.

As noted previously, conventional therapies, i.e., systemic deliveries of anti-malarials, especially by oral administration, suffer from significant failings. For example, when HCQ is delivered through the conventional systemic routes, there is a significant delay in the onset of the anti-malarial action, due to active concentration of the therapeutic agent in certain organs, which are often not the target organ. Moreover, long-term high dose use has been shown to carry a risk of serious side effects, including retinal damage.

Nevertheless, it was thought heretofore that systemic delivery was necessary to achieve a therapeutic effect. Thus, like other anti-inflammatory pharmaceuticals, anti-malarial compounds have uniformly been prescribed systemically, typically by oral dosing.

The present invention is the first to demonstrate that targeted delivery of an anti-malarial compound to an internal organ, via mucosal, serosal, or synovial application, for example, is effective in treating inflammatory conditions. The inventor has found, unexpectedly, that localized delivery of anti-malarial compounds maintains or improves therapeutic value, while avoiding the problems associated with conventional treatment regimes.

Also unexpected is the inventor's demonstration that locally delivered anti-malarial compounds, such as HCQ,

have potent anti-asthmatic effects, including anti-bronchospastic effect, effectively blocking early phase allergic response, and ablation of late-phase allergic response. Inhaled anti-malarial compounds, such as HCQ, are well tolerated as evidenced by the lack of increase in airway resistance after inhalation, demonstrating that the nebulized form is not a bronchial irritant and, hence, is suitable for administration via inhalation. Moreover, the local administration of the anti-malarial compounds significantly reduces and/or eliminates the toxic side-effects of these compounds which are manifested when given by systemic administration, such as by oral administration. The major toxicity of this class of pharmaceuticals when given systemically is related to the selective accumulation of the drug in the retina and subsequent binding of melanin which may lead to retinal photoreceptor damage. This may lead to retinal damage. Other side effects associated with hydroxychloroquine therapy include nausea, anorexia, diarrhea, pruritus, urticaria, increased skin pigmentation, exfoliative dermatitus, headache, and scotomata. By administering the antimalarial, such as HCQ locally, such by inhalation, less drug is required and therefore either the patient does not experience the aforementioned side effects or, if experienced, they are significantly less severe.

Relative to systemic administration, such as oral administration, the present invention has significant benefits over available oral or systemically administered routes, such as a more rapid accumulation of therapeutic amounts of compound in the tissue which is targeted, as well as a rapid onset of action, measured in days as opposed to months. Localized delivery results in reduced dosage requirements, both daily and cumulatively, and minimizes side effects.

The low-dose, targeted, and organ-oriented approach of the instant invention minimizes all the drawbacks of the systemic approach, such as increased cost for the medicine and inconvenience to the patients, resulting from prolonged and high dose usage.

The anti-malarial compounds of the invention, especially, aminoquinoline derivatives, are, without wishing to be bound, believed to be particularly effective because they are multi-factorial inhibitors, blocking both humoral and cell-mediated/delayed response immune systems. Anti-malarial compounds, such as aminoquinoline derivatives, appear to exert their pharmacologic effects due to several underlying properties. For example, see MacKenzie, 1983, *Am J Medicine* 75:1A:5–10; Fox, 1993, *Sem. Arthritis Rheumatism* 23:82–91.

These properties seem to result from the unique effect on membranes of compounds in this group. Without wishing to be bound, it is believed that anti-malarial compounds, such as aminoquinoline derivatives, are able to elevate intravesical pH by intracellularly concentrating in acidic cytoplasmic vesicles in a variety of immune function cells. Since several processes critical for the generation of immune response depends on neutral or acidic pH environments, this action inhibits cellular functions in mature cells such as lymphocytes, monocytes, neutrophils and macrophages which depend on an active lysosomal system.

Interference with vesical fusion decreases secretion and release of intracellular products, such as immunoglobins including IgE (allergic antibody), interleukins and cytokines used in signaling and augmenting immune responses (e.g., IL-1, IL-6, TNF-α, ICAM-1, IL-4), exocytosis of lysosomal products such as superoxides in neutrophils and macrophages. Similarly, such interference also decreases efficiency of phagolysosomal system by inhibiting production of superoxides in neutrophils. Furthermore, increases of lysosomal pH interfere with lysosomal acid hydrolases. As a consequence of these actions, antigen processing is inhibited.

Furthermore, the interference with vesical fusion causes depletion of surface receptors due to sequestion of plasma membranes in stabilized intercellular vesicles. This leads to depletion of cell surface markers necessary for antigen presentation, immune recognition, and cellular responsiveness. As a result, T-cell activation is inhibited, and interleukin responses antagonized. For example, HCQ blocks the actions of IL-4 (Seggev J Immunol 150:62A), an interleukin both critical for the recruitment of eosinophils, a primary effector cell in asthmatic inflammation, and for the generation of IgE allergic antibody.

The depletion of cell surface markers has been reported to reduce the transmission of a number of viruses including rhinovirus and adenovirus. In part, this may be dne to known reduction of membrane receptors, such as ICAM-1, which are critical for viral uptake. Interference with the phagolysosomal system may help explain an observed decrease in viral replication for other viruses including HIV and influenza.

Cumulatively, the result of anti-malarial compound, including aminoquinoline derivative, inhibition of antigen presentation and T-cell activation is a reduction in delayed hypersensitivity (cell-mediated) responses, modulation of humoral responses, decreases in viral uptake and replication, modulation and/or suppression of early and late phase allergic response, and inhibition of inflammatory effector cell function. Finally, derivatives of anti-malarials, including aminoquinolines, are reported to block viral replication and transmission (for example, of rhinovirus and adenovirus) and to have anti-brochospastic effects.

The inventor has found that each of the effects noted above can be accomplished via localized delivery, for example, by application of the anti-malarial compounds to musocal, serosal, or synovial application and uptake.

In sum, anti-malarial compounds such as the aminoquinoline derivatives have beneficial effects with respect to a wide range of inflammatory diseases, including granulomatous, neutrophil, mast cell, eosinophil, basophil, and macrophage-mediated inflammation as well as humoral antibody mediated-inflammation. The ability of these multifactorial agents to modify a wide range of local responses supports their use of localized delivery to sclera, nasal or oral mucosa, bronchial epithelium, or lower intestine and sigmoid colon, because these inflammatory manifestations all have in common the participation of immune cells which generate a local inflammatory response, despite other differences among these inflammatory conditions. For each of these illnesses, localized delivery has the same advantages, including more rapid onset of action at less risk due to lower cumulative and daily doses.

Therapeutic Methodology

In accordance with the present invention, a therapeutic composition as described above, typically is applied to patients suffering from an inflammatory condition. Inflammatory conditions usually are characterized by an activation of the immune system, such as T-cell activation. Such activation often is mediated by effector cells, such as neutrophils, macrophages or eosinophils, and may be promoted by specific mediators such as IL-1, Il-4 or TNF or allergic antibodies. Some inflammatory conditions involve cell-mediated granulomatous inflammation.

Thus, a patient in this context often will suffer from a disorder characterized by one or more of the foregoing signs of an inflammatory condition. By the same token, the present invention entails localized administration, to a patient in need, of an anti-malarial compound, formulated along the lines detailed above, in an amount that alleviates or ameliorates a symptom or the underlying pathology of an inflammatory condition ("an effective amount" or "anti-inflammatory effective amount").

Specific examples of inflammatory conditions treatable according to the invention include, but are not limited to, scleritis; epi-scleritis; allergic conjunctivitis; pulmonary inflammatory diseases, particularly asthma, chronic obstructive pulmonary disease (COPD), allergic bronchopulmonary aspergillosis (ABPA), and sarcoidosis; procto-sigmoiditis; allergic rhinitis; arthritis; tendonitis; apthous stomatitis; and inflammatory bowel disease.

The compound may be administered by any suitable means, as described hereinabove depending on the condition being treated. For example, in treating ocular diseases, such as scleritis and epi-scleritis or allergic conjunctivitis, the compound may be administered as a topical ophthalmic preparation. On the other hand, it may be compounded as nasal spray or mist for inhalation in treating allergic rhinitis. Treating apthous stomatitis advantageously employs an oral paste. Parenteral injections are suitable for the localized treatment of arthritis or tendonitis. Procto-sigmoiditis, and the like, will usually be treated with an appropriately formulated retention enema. Asthmatic and non-asthmatic pulmonary conditions, such as COPD, and ABPA, may be and preferably are treated by inhalation of a suitable composition.

As used herein, the plural signifies the singular and vice-versa.

Moreover, in the chemical formula described hereinabove, if not specifically drawn, it is to be understood that if a central atom does not have all the valences, the remaining bonds are to hydrogen atoms.

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. In addition, throughout the specification, any and all references to publicly available documents are specifically incorporated by reference.

Animal Studies of the Effect of Nebulized HCQ on Asthma

Using a well established animal model of asthma employing Ascaris-sensitized sheep (Abraham, et al., *Am. J. Respir. Crit. Care Med.*, 1997, 156:696–703), the contents of which are incorporated by reference, the inventor completed animal experiments investigating the effect of nebulized HCQ on early and late allergic asthmatic responses to antigen challenge. These studies confirm that targeted and localized delivery of HCQ has potent anti-asthmatic effects. In addition, quite unexpectedly, local delivery, in this case administered via nebulized aerosol, resulted in more rapid onset of drug effect than in oral administration and at significantly lower dosage levels, both daily and cumulatively.

Inhaled HCQ partially blocks immediate allergic-mediated bronchostrictive responses, virtually eliminates late-phase responses which occur on four to 12 hours post-antigen challenge, and moreover, shows continued effect at blocking the bronchial hyperresponsiveness even twenty-four hours later after local administration of the anti-malarial compound. Because late phase allergic inflammatory responses is the most complete representation of the bronchial inflammation that characterizes asthma, these findings underline the potent local anti-inflammatory capabilities of anti-malarial compounds, e.g., aminoquinolines like HCQ, which do not rely on its systemic effects, but rather are generated in an organ-specific manner (in this case the bronchial airways) when delivered by inhalation.

METHODS FOR EXAMPLES 1–2

All procedures were approved by the Mount Sinai Medical Center Animal Research Committee, which is responsible for assuring the humane care and use of experimental animals. The sheep used for this study had previously been shown to develop early and late airway responses and airway hyperresponsiveness to inhaled carbachol following inhalation challenge with *Ascaris suum* antigen.

Measurement of Airway Mechanics: The unsedated sheep were restrained in a cart in the prone position with their heads immobilized. After topical anesthesia of the nasal passages with 2% lidocaine solution, a balloon catheter was advanced through one nostril into the lower esophagus. The animals were incubated with a cuffed endotracheal tube through the other nostril using a flexible fiberoptic bronchoscope as a guide. (The cuff of the endotracheal tube was inflated only for the measurement of airway mechanics and during aerosol challenges to prevent undue discomfort. This procedure has no effect on airway mechanics). Pleural pressure was estimated with the esophageal balloon catheter (filled with one ml of air) which was positioned 5–10 cm from the gastroesophageal junction. In this position, the end expiratory pleural pressure ranged between −2 and −5 cm H_2O. Once the balloon was placed, it was secured so that it remained in position for the duration of the experiment. Lateral pressure in the trachea was measured with a sidehole catheter (inner dimension, 2.5 mm) advanced through and positioned distal to the tip of the endotracheal tube. Transpulmonary pressure, the difference between tracheal and pleural pressure, was measured with a differential pressure transducer catheter system. For the measurement of pulmonary resistance (R_L), the proximal end of the endotracheal tube was connected to a pneumotachograph (Fleisch No. 1; Dyna Sciences, Inc., Blue Bell, Pa.). The transpulmonary pressure and flow signals were recorded on a multichannel physiologic recorder, which was linked to an 80–386 DOS Personal Computer (CCI Inc., Miami, Fla.) for on-line calculation of mean pulmonary flow resistance (RL) by dividing the change in transpulmonary pressure by the change in flow at mid-tidal volume (V_T) (obtained by digital integration). The mean of at least five breaths, free of swallowing artifact, was used to obtain R_L in cm H_2O/L/s. Immediately after the measurement of R_L, thoracic gas volume (Vtg) was measured in a constant-volume body plethysmograph to obtain specific lung resistance ($SR_L = R_L \times V_{tg}$) in Lxctn H_2O/L/s.

Aerosol Delivery Systems: Aerosols of *Ascaris suum* extract (diluted 20:1 with phosphate buffered saline; 82,000 PNU/ml) were generated using a disposable medical nebulizer (Raindrop®, Puritan Bennett), which produces an aerosol with a mass median aerodynamic diameter of 3.2 μm (geometric standard deviation, 1.9) as determined by a 7 stage Andersen cascade impactor. The output from the nebulizer was directed into a plastic T-piece, one end of which was connected to the inspiratory port of a Harvard respirator. To better control aerosol delivery, a dosimeter consisting of a solenoid valve and a source of compressed air (20 psi) was activated at the beginning of the inspiratory

cycle of the Harvard respirator system for 1 second. The aerosol was delivered at a tidal volume of 500 ml and a rate of 20 breaths per minute for 20 minutes. Each sheep was challenged with an equivalent dose of antigen (400 breaths) in the control and drug trials. Carbachol aerosols were also generated with this same nebulizer system.

Dose Response Curves to Inhaled Carbachol: For the carbachol dose response curves, measurements of SR_L were repeated immediately after inhalation of buffer and after each administration of 10 breaths of increasing concentrations of carbachol solution (0.25%, 0.5%, 1.0%, 2.0% and 4.0% w/v). To assess airway responsiveness, the cumulative carbachol dose in breath units (BU) that increased SR_L 400% over the post-buffer value (i.e. PC_{400}) was calculated from the dose response curve. One breath unit was defined as one breath of a 1% w/v carbachol solution.

Bronchial Biopsies

Bronchial biopsies were done before the initiation of treatment and 24 h after antigen challenge. Pre- and postchallenge biopsy specimens were obtained from opposite lungs, and at least three specimens were obtained from each lung at each time point. Biopsy specimens were fixed in 10% buffered formalin and processed routinely for puraffin embedding. Tissue sections (4 μm) were stained with Giemsa, using the microwave method described in Churukian, 1995, *J. Histotech.*, 18:319–322, the content of which are incorporated by reference. This technique gives more uniform staining and better contrast between nuclei and cytoplasm. Parallel sections were stained with toluidine blue for identification of meta-chromatic-staining cells (most cells/basophils). Slides were examined with a BH2 light microscopic (Olympus Corp., Tokyo, Japan) equipped with differential interference contrast optics, using a calibrated eye piece grid (10x10), which covered 1,600 μm^2 with a X40 objective. The number and distribution of inflammatory cells (polymorphonuclear leukocytes [PMN], lymphocytes, eosinophils, and mast cells/basophils) was assessed in bronchial epithelium and lamina propria. A minimum of five fields from each biopsy were examined, the number of cells for each cell type were averaged for the five fields, and the results were expressed as number of cells/grid.

Agents

Ascaris suum extract (Great Diagnostics, Lenor, N.C.) was diluted with PBS to a concentration of 82,000 protein nitrogen units/ml and delivered as an aerosol (20 breaths/minx20 min). This crude preparation has an endotoxin level of 50 Eu/ml, which does not have a pulmonary effect in sheep. Carbamylcholine (Carbachol; Sigma Chemical Co., St. Louis, Mo.) was dissolved in buffered saline at concentrations of 0.25, 0.50, 1.0, 2.0 and 4.0% wt/vol and delivered as an aerosol.

EXAMPLE 1

At 3 to 4 days before treatment was begun, baseline airway responsiveness, to aerosol carbachol (i.e., PC_{400}) was determined and a baseline bronchial biopsy performed. Then at 4 days before antigen challenge, the asthmatic sheep began treatment with 30 mg an average of 0.78 mg/kg HCQ (30 mg/animal, 30 mg in 5 cc Normal Saline, given as aerosol). The animals were treated two times a day for 3 days and then, on the fourth day, at 0.5 hours before antigen challenge and again at 4 hours after challenge. On the antigen-challenge day, SR_L was measured and the animals were than treated with HCQ designated compound. SR_L was remeasured 0.5 h after treatment (just before challenge) and the animals were then challenged with antigen. SR_L was then remeasured immediately after.

The results were compared to those obtained with the sheep to which PBS were administered in lieu of the drug and challenged in the same fashion. The results are tabulated in Table 1 and graphically represented in FIG. **1**.

The results indicate that application of HCQ in aerosolized form does not cause any major irritant effects. For example, specific resistance, obtained pre- and immediately following HCQ application, showed no change following antigen challenge (see FIG. **1** and Table 1). Specific resistance rose an average of 232% in the control group but only 95% in the treated group. This effect is similar to that seen with other available anti-asthmatic drugs, such as inhaled budesonide (Abraham, W. M., Late phase responses in the sheep, in Airways smooth muscle: modeling the asthmatic responses in vivo, ed., D. Raeburn and M A Giembycz, Birkauser, Boston).

EXAMPLE 2

In a second experiment, the procedure of Example 1 was followed except the animals received a dosage of an average of 40 mg b.i.d. (2 mg/kg/day) of HCQ for 3 days. On the fourth day, they received an additional treatment one-half hour prior to antigen challenge. While acute reactions were not inhibited, late phase asthmatic reactions were virtually completely blocked in the drug-treatment group. Specific resistance in the control group peaked at an increase of a mean of 148% at 6.5 hours, compared to a mean increase of only 14% in the drug-treated group. See FIG. **2** and Table 2.

Underlining the potent effect of the HCQ treatment, a 24 hour post-antigen challenge carbachol reactivity (PC 400 as measured in breath units) increased in the control group by 50% as anticipated, but actually fell in the treatment group from 12.74 to 15.82 units (see FIG. **3**).

TABLE 1

Specific resistance following antigen challenge (Example 1)

Sheep No.	BSLN. Srl	p-pl/dg Srl	p-pl/dg %	p-pl/dg Srl	p-pl/dg %	P-ASC Srl	P-ASC %	+1 HR Srl	+1 HR %	+2 HRS Srl	+2 HRS %	+3 HRS Srl
CONTROL TRIAL: (immediate) (just before Ag)												
933	0.94	0.94	0%	0.94	0%	3.4	262%	1.14	21%	1.1	17%	
1483	1.17	1.17	0%	1.17	0%	3.54	203%	1.19	2%	1.15	22%	

TABLE 1-continued

Specific resistance following antigen challenge (Example 1)

Sheep No.	BSLN. Srl	p-pl/dg Srl	p-pl/dg %	p-pl/dg Srl	p-pl/dg %	P-ASC Srl	P-ASC %	+1 HR Srl	+1 HR %	+2 HRS Srl	+2 HRS %	+3 HRS Srl
1530	1.05	1.05	0%	1.05	0%	2.5	138%	1.54	47%	1.02	−3%	
Mean :	1.06	1.06	0%	1.06	0%	3.47	232%	1.17	11%	1.13	20%	0.00
SE :	0.12	0.12	0%	0.12	0%	0.07	30%	0.03	10%	0.02	2%	0.00
COMPOUND TRIAL												
933	1.02	1.20	18%	1.11	9%	2.45	140%	1.35	32%	1.13	11%	
1483	1.00	1.02	2%	0.95	−5%	1.49	49%	1.43	43%	1.74	74%	
1530	1.15	1.37	19%	1.13	−2%	3.32	189%	1.49	30%	1.2	4%	
Mean :	1.01	1.11	10%	1.03	2%	1.97	95%	1.39	38%	1.44	42%	0.00
SE :	0.01	0.09	8%	0.08	7%	0.48	46%	0.04	5%	0.31	32%	0.00

TABLE 2

Specific resistance following antigen challenge (Example 2)

Sheep No.	BSLN. Srl	p-pl/dg Srl	p-pl/dg %	p-pl/dg Srl	p-pl/dg %	P-ASC Srl	P-ASC %	+1 HR Srl	+1 HR %	+2 HRS Srl	+2 HRS %	+3 HRS Srl
CONTROL TRIAL: (immediate) (just before Ag)												
1125	1.04	1.04	0%	1.04	0%	3.24	212%	2.41	132%	2.1	92%	1.89
1534	1.11	1.11	0%	1.11	0%	4.03	263%	2.85	157%	1.99	79%	1.96
Mean :	1.08	1.08	0%	1.08	0%	3.64	237%	2.63	144%	2.00	86%	1.93
SE :	0.04	0.04	0%	0.04	0%	0.40	26%	0.22	13%	0.01	7%	0.04
COMPOUND TRIAL												
1125	1.02	1.15	13%	0.96	−6%	3.02	196%	2.76	171%	2.06	102%	1.57
1534	1.09	1.01	−7%	1.17	7%	4.14	280%	2.10	93%	1.48	36%	1.59
Mean :	1.06	1.08	3%	1.07	1%	3.58	238%	2.43	132%	1.74	69%	1.58
SE :	0.04	0.07	10%	0.11	7%	0.56	42%	0.33	39%	0.29	33%	0.01

Sheep No.	+3 HRS %	+4 HRS Srl	+4 HRS %	+5 HRS Srl	+5 HRS %	+6 HRS Srl	+6 HRS %	+6 HRS Srl	+6 HRS %	+7 HRS Srl	+7 HRS %
CONTROL TRIAL: (immediate) (just before Ag)											
1125	82%	1.14	10%	1.73	66%	2.65	155%	2.65	155%	2.68	158%
1534	77%	1.59	43%	1.95	76%	2.08	87%	2.68	141%	2.12	91%
Mean :	79%	1.37	26%	1.84	71%	2.37	121%	2.67	148%	2.40	124%
SE :	3%	0.23	17%	0.11	5%	0.28	34%	0.02	7%	0.28	33%
COMPOUND TRIAL											
1125	54%	1.12	10%	1.39	36%	1.22	20%	1.10	8%	1.22	20%
1534	46%	1.39	28%	1.07	−2%	1.26	16%	1.32	21%	1.23	13%
Mean :	50%	1.26	19%	1.23	17%	1.24	18%	1.21	14%	1.23	16%
SE :	4%	0.13	9%	0.16	19%	0.02	2%	0.11	7%	0.01	3%

SHEEP No.	+7.5 HRS Srl	+7.5 HRS %	+8 HRS Srl	+8 HRS %	ORC #1 BSLN.	ORC #2 (24 P-Ag.)
CONTROL TRIAL: (immediate) (just before Ag)						
1125	2.42	133%	1.71	64%	18.04	9.76
1534	2.11	90%	1.94	75%	13.98	7.48
Mean :	2.26	111%	1.83%	70%	16.01	8.62
SE :	0.16	21%	0.12	5%	2.03	1.14
COMPOUND TRIAL						
1125	1.53	50%	1.24	22%	10.65	15.86
1534	1.30	19%	1.29	18%	14.83	15.77
Mean :	1.42	35%	1.27	20%	12.74	15.82
SE :	0.12	15%	0.03	2%	2.09	0.04

METHODS OF EXAMPLE 3

All procedures were approved by the Mount Sinai Medical Center Animal Research Committee, which is responsible for assuring the humane care and use of experimental animals. The sheep used for this study had previously been shown to develop early and late airway responses and

airway hyperresponsiveness to inhaled carbachol following inhalation challenge with *Ascaris suum* antigen. During the chronic treatment trail, venous blood samples were obtained from the external jugular vein for the determination of plasma compound concentrations. Samples were obtained as baseline (pre-dosing), and, then, before dosing on days 8, 15, 22, 29 and after dosing had stopped on day 43.

Measurement of Airway Mechanics: The unsedated sheep were restrained in a cart in the prone position with their heads immobilized. After topical anesthesia of the nasal passages with 2% lidocaine solution, a balloon catheter was advanced through one nostril into the lower esophagus. The animals were incubated with a cuffed endotracheal tube through the other nostril using a flexible fiberoptic bronchoscope as a guide. (The cuff of the endotracheal tube was inflated only for the measurement of airway mechanics and during aerosol challenges to prevent undue discomfort. This procedure has no effect on airway mechanics). Pleural pressure was estimated with the esophageal balloon catheter (filled with one ml of air) which was positioned 5–10 cm from the gastroesophageal junction. In this position, the end expiratory pleural pressure ranged between −2 and −5 cm H_2O. Once the balloon was placed, it was secured so that it remained in position for the duration of the experiment. Lateral pressure in the trachea was measured with a sidehole catheter (inner dimension, 2.5 mm) advanced through and positioned distal to the tip of the endotracheal tube. Transpulmonary pressure, the difference between tracheal and pleural pressure, was measured with a differential pressure transducer catheter system. For the measurement of pulmonary resistance (R_L), the proximal end of the endotracheal tube was connected to a pneumotachograph. The signals of flow and transpulmonary pressure were recorded on a n oscilloscope recorder which was linked to a computer for on-line calculation of R_L from transpulmonary pressure, respiratory volume (obtained by digital integration) and flow. Analysis of 5–10 breaths were used for the determination of R_L. Immediately after the measurement of R_L, thoracic gas volume (V_{tg}) was measured in a constant volume body plethysmograph to obtain specific lung resistance ($SR_L=R_L \cdot V_{tg}$) in cm $H_2O \cdot sec^{-1}$.

Aerosol Delivery Systems: Aerosols of Ascaris suum extract (diluted 20:1 with phospbate buffered saline; 82,000 PNU/ml) were generated using a disposable medical nebulizer (Raindrop®, Puritan Bennett), which produces an aerosol with a mass median aerodynamic diameter of 3.2 μm (geometric standard deviation, 1.9) as determined by a 7 stage Andersen cascade impactor. The output from the nebulizer was directed into a plastic T-piece, one end of which was connected to the inspiratory port of a Harvard respirator. To better control aerosol delivery, a dosimeter consisting of a solenoid valve and a source of compressed air (20 psi) was activated at the beginning of the inspiratory cycle of the Harvard respirator system for 1 second. The aerosol was delivered at a tidal volume of 500 ml and a rate of 20 breaths per minute for 20 minutes. Each sheep was challenged with an equivalent dose of antigen (400 breaths) in the control and drug trials. Carbachol aerosols were also generated with this same nebulizer system.

Dose Response Curves to Inhaled Carbachol: For the carbachol dose response curves, measurements of SR_L were repeated immediately after inhalation of buffer and after each administration of 10 breaths of increasing concentrations of carbachol solution (0.25%, 0.5%, 1.0%, 2.0% and 4.0% w/v). To assess airway responsiveness, the cumulative carbachol dose in breath units (BU) that increased SR_L 400% over the post-buffer value (i.e. PC_{400}) was calculated from the dose response curve. One breath unit was defined as one breath of a 1% w/v carbachol solution.

EXPERIMENTAL PROTOCOL

The same basic protocol was used for all studies in Example 3. This basic protocol consisted of first obtaining baseline dose response curves to aerosol carbachol 1–3 days prior to antigen challenge. Then, on the day of antigen challenge, values of specific lung resistance (SR_L) were measured at baseline and, then, 30 min after drug or vehicle (0.9% saline) treatment. The animals were, then, challenged with Ascaris suum antigen and SR_L was remeasured immediately after challenge, hourly from 1–6 h after challenge and on the half-hour from 6½–8 h after challenge. Measurements of SR_L were obtained 24 h after challenge followed by the 24 h post challenge dose response curve.

Studies differed in time of treatment, treatment dose or route of administration. In the first series, animals were treated with 1 mg/kg HCQ (dissolved in 5 ml 0.9% saline) by aerosol twice a day for 3 days and, then, on again on the 4th (antigen challenge day) 30 min before and 8 h after antigen challenge. A second control challenge was done 2 weeks after the drug trial to insure that the 4 day treatment regimen had no carry-over effect. In the second series, this same treatment regimen was used except the sheep received HCQ, p.o (1 mg/kg in 10 ml 0.9% saline). A second control challenge was done 2 weeks after the drug trial to insure that the 4 day treatment regimen had no carry-over effect. In the third series of studies, sheep were treated with 2 mg/kg HCQ (dissolved in 5 ml 0.9% saline) by aerosol, once a day for 3 days and, then, on again on the 4th (antigen challenge day) 30 min before antigen challenge. A second control challenge was done 2 weeks after the drug trial to insure that the 4 day treatment regimen had no carry-over effect. In the fourth series, the 4 day single treatment protocol was used, and the sheep used in the third series of experiments were treated with 0.2 mg/kg HCQ aerosol and 0.6 mg/kg HCQ aerosol (both dissolved in 5 ml 0.9% saline). Challenges were separated by 2 weeks. In the fifth series, sheep were challenged with 2 mg/kg HCQ aerosol (dissolved in 5 ml 0.9% saline), once a day for 14 days. On the 15th day, the animals were treated and 30 min later, challenged with antigen. On the following day, after determining the post challenge PC_{400}, the animals resumed treatment for another 14 days, after which, they were challenged with antigen (day 29). The animals were then left untreated for 14 days, after which an antigen challenge was conducted (day 43) and, then, this procedure was repeated after another 2 weeks (day 57).

STATISTICAL ANALYSIS

For each series, a repeated measures analysis of variance was performed to see if there were overall differences between the historical control the drug trial and the 2 week follow-up control or, in the case of experiments described in series 4 and 5, amongst the doses and different times, respectively. If a significant overall effect was found, then a two-tailed paired t-test were used to assess pairwise differences. The variables assessed were the peak early airway response (maximum increase in SR_L 0–4 h after challenge), peak late airway response (maximum increase in SR_L between 5–8 h after antigen challenge, irrespective of when this increase occurred for each sheep in each trial) and on the ratio of post challenge PC_{400} to pre challenge PC_{400}. (Note: a ratio close to 1 indicates no airway hyperresponsiveness, whereas, a ratio close to 0.5 indicates the development of airway hyperresponsiveness.). Peak responses were used

because they are the most conservative estimate of the overall effect. Values in the text and figures are mean±se for 3 sheep. Statistical analysis of these variables is reported in Table 3.

RESULTS

1 mg/kg HCQ Aerosol Twice a Day for 4 Days.

FIG. **4A** illustrates the time course of the antigen-induced responses and FIG. **4B** the effects on airway responsiveness in the three sheep treated with HCQ aerosol. There was no effect on the early airway response (EAR), however, HCQ aerosol blocked the late airway response (LAR) to allergen in these animals (ANOVA, $P<0.001$). Consistent with the protection against the late response was the protection against the airway hyperresponsiveness (AHR, ANOVA, $P=0.011$). Note that 2 weeks after treatment was stopped, the animals responded normally to allergen.

1 mg/kg HCQ, p.o. Twice a Day for 4 Days.

FIG. **5A** illustrates the time course of the antigen-induced responses and FIG. **5B** the effects on airway responsiveness in the three sheep treated with oral HCQ. Unlike when given by inhalation, oral treatment did not protect against the antigen-induced EAR, LAR or AHR.

Thus, the procedures in Series 1 and 2 and the data in FIGS. **4A**, **4B**, as compared to the data in FIGS. **5A** and **5B** show that local administration of HCQ greatly enhances the efficacy of the HCQ relative to systemic administration thereof, such as by oral administration.

2 mg/kg HCQ Aerosol Once a Day for 4 Days.

FIG. **6A** illustrates the time course of the antigen-induced responses and FIG. **6B** the effects on airway responsiveness in the three sheep treated once a day with HCQ aerosol. There was no effect on the EAR, however, HCQ aerosol blocked the LAR to allergen in these animals (ANOVA, $P=0.001$). Consistent with the protection against the late response was the protection against the antigen-induced AHR (ANOVA, $P=0.026$). Note that, 2 weeks after treatment was stopped, the animals responded normally to allergen. This shows that dosing by inhalation may be limited to once a day formulation.

Dose Response to Aerosol HCQ.

FIG. **7A** illustrates the time course of the antigen-induced responses and FIG. **7B** the effects on airway responsiveness in the three sheep treated with different doses of HCQ aerosol. There was no effect on the EAR, however, HCQ aerosol blocked the LAR to allergen in these animals (ANOVA, $P=0.007$). Consistent with the protection against the late response was the protection against the antigen-induced AHR (ANOVA, $P=0.011$). Overall, 0.6 mg/kg had significant protective effects in this trial. To get a better estimate of the dose-response relationship, the average LAR (between 5–8 h) for each dose was calculated, and this value was used to determine a mean percent protection. Likewise, the mean values for AHR shown in Table 3 were used to calculate the mean percent protection provided by each dose on this parameter. These results are shown in FIG. **8**.

Effect of Chronic Treatment with Aerosol HCQ.

FIG. **9A** illustrates the time course of the antigen-induced responses and FIG. **9B** the effects on airway responsiveness in the three sheep treated with HCQ aerosol for up to 4 weeks. Overall, there was no effect on the EAR. HCQ aerosol did block the LAR to allergen in these animals (ANOVA, $P=0.002$). Consistent with the protection against the late response was the protection against the antigen-induced AHR (ANOVA, $P=0.018$). While it was expected that the 2 and 4 week treatments would be effective in blocking the LAR and AHR, the unexpected result was the carryover effect on these variables seen 2 weeks after treatment had stopped. The effect was more pronounced on the LAR as compared to the AHR. By 4 weeks, the animals' responses had returned to normal. The effect of the different treatment and recovery times on the percent protection of the LAR and AHR are seen in FIG. **10** (calculations were made as described previously). As can be seen, the mean percent protection for both variables increased with treatment time. Likewise, in this protocol, there was still a good protective effect two weeks after stopping drug treatment.

These results show that the dosing strategy in daily dosing may be reduced after a short period of time.

TABLE 3[a]

TREATMENT	BASELINE	EAR[b]	LAR[b]	AHR[c]
Control 1	0.93 ± 0.03	5.74 ± 1.48	2.88 ± 0.24	0.43 ± 0.07
HCQ (aerosol) 1 mg/kg/dx2 x4d	0.93 ± 0.01	5.57 ± 1.82	1.35 ± 0.15[d,e]	0.90 ± 0.06[d,g]
Control 2	0.97 ± 0.03	6.27 ± 1.39	2.86 ± 0.32	0.50 ± 0.48
Control 1	1.06 ± 0.04	4.64 ± 0.58	2.72 ± 0.47	0.49 ± 0.07
HCQ (p.o.) 1 mg/kg/dx2 x4d	0.96 ± 0.01	4.64 ± 0.55	2.27 ± 0.10	0.46 ± 0.06
Control 2	0.98 ± 0.03	4.08 ± .47	2.59 ± 0.34	0.48 ± 0.10
Control 1	1.01 ± 0.03	4.36 ± 0.48	2.6 ± 0.12	0.45 ± 0.08
HCQ (aerosol) 2 mg/kg/dx4 d	0.93 ± 0.03	3.5 ± 0.73	1.34 ± 0.32[d,e]	1.05 ± 0.14[e]
Control 2	0.95 ± 0.01	4.38 ± 0.38	2.35 ± 0.17	0.45 ± 0.04
Control	0.95 ± 0.01	4.38 ± 0.38	2.35 ± 0.17	0.45 ± 0.04
HCQ (aerosol) 2 mg/kg/dx4 d	0.93 ± 0.02	3.53 ± 0.73	1.34 ± 0.03[d]	1.05 ± 0.14[d]
HCQ (aerosol) 0.2 mg/kg/d x4d	0.92 ± 0.02	3.95 ± 0.47	2.22 ± 0.17[h]	0.53 ± 0.06[j]

TABLE 3[a]-continued

TREATMENT	BASELINE	EAR[b]	LAR[b]	AHR[c]
HCQ (aerosol) 0.6 mg/kg/d x4d	0.93 ± 0.02	3.19 ± 0.51	1.30 ± 0.18[d]	0.84 ± 0.15
Control	0.97 ± 0.03	6.27 ± 1.39	2.39 ± 0.17	0.50 ± 0.05
HCQ (aerosol) 2 mg/kg/dx1 4d	0.91 ± 0.03	4.21 ± 1.68	0.78 ± 0.39[d]	0.85 ± 0.07[g]
HCQ (aerosol) 2 mg/kg/dx2 8d	1.01 ± 0.01	4.21 ± 1.16	1.22 ± 0.08[e]	0.94 ± 0.02[g]
No Treatment 14d	1.00 ± 0.06	4.17 ± 1.70	1.69 ± 0.21	0.67 ± 0.16
No Treatment 28d	0.97 ± 0.02	4.35 ± 0.74	2.69 ± 0.26[h]	0.39 ± 0.11[h]

[a]All results are presented as mean ± SE for n = 3.
[b]Values for baseline, peak EAR (largest value of specific lung resistance for each sheep between 0–4h) and peak LAR (largest value of specific lung resistance for each sheep between 5–8h, irrespective of the time at which it occurred) are specific lung resistance in $cmH_2O.sec^{-1}$.
[c]Values for AHR are post challenge PC_{400}/ Pre-challenge PC_{400} ratio. A value close to 1 indicates that there is no change in airway responsiveness. Values less than 1 indicate the development of AHR.
[d]P < 0.05 vs Control 1;
[e]vs Control 2, P < 0.05 vs
[f]Control 1,
[g]Control 2; P < 0.10 vs
[h]Control 1,
[i]Control 2; P < 0.05 vs
[j]largest dose; P < 0.10 vs
[k]largest dose,

Conclusion

The examples above confirm in an allergic sheep model that an anti-malarial agent, when administered locally, such as inhaled hydroxychloroquine, has potent local anti-inflammatory effects and achieves rapid onset of action at lower daily and cumulative dosage than would be expected from systemic administration.

The above preferred embodiments and examples are given to illustrate the scope and spirit of the present invention. These embodiments and examples will make apparent to those skilled in the art other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention.

Therefore, the present invention should be limited only by the appended claims.

What is claimed:

1. A method for treating an inflammatory condition in an animal comprising administering locally to the area of inflammation to said animal an anti-inflammatory effective amount of an anti-malarial compound, wherein said anti-malarial compound is hydroxychloroquine or a pharmaceutically acceptable salt thereof.

2. The method according to claim **1**, wherein the inflammatory condition is selected from the group consisting of an inflammatory pulmonary disease, scleritis, epi-scleritis, allergic conjunctivitis, procto-sigmoiditis, allergic rhinitis, arthritis, tendonitis, apthous stomatitis, and inflammatory bowel disease.

3. The method according to claim **2** wherein the inflammatory pulmonary disease is selected from the group consisting of asthma, chronic obstructive pulmonary disease, allergic bronchopulmonary aspergillosis, and sarcoidosis.

4. The method according to claim **1**, wherein the anti-malarial compound is locally administered to the lungs.

5. The method according to claim **4**, wherein the anti-malarial compound is locally administered via inhalation.

6. The method according to claim **5**, wherein the anti-malarial compound is formulated for aerosol delivery or formulated as dry powder.

7. The method according to claim **1** wherein the inflammatory condition is asthma.

8. The method according to claim **1**, wherein the anti-malarial compound is formulated as an eye drop, a suppository, a nasal spray, or an oral paste.

9. A method for treating asthma, comprising administering an anti-inflammatory effective amount of hydroxychloroquine via inhalation to a patient with asthma.

* * * * *

From:	Lambert, Linda (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CE6824B6A92A4A4E893EA7B54E17EB3C-LAMBERT, LI <Linda.Lambert@hhs.gov>
To:	Kane, Elleen (OS/ASPR/OEA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=user25dbd6c7 <Elleen.Kane@hhs.gov>; Waters, Cicely (OS/ASPR/OEA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00e638c4ddf64006bcc009e8032dd700-Waters, Cic <Cicely.Waters@hhs.gov>; ASPRMEDIA (OS/ASPR/COO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1949c96e6c46444383366c69b467cec1-ASPRMEDIA@h <ASPRMEDIA@hhs.gov>
CC:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04528b7c91bbd61893975-Houchens, C <Christopher.Houchens@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>; Faison, Tremel (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2bbab0bceb1342fbbedbbcc94deeb80f-Faison, Tre <Tremel.Faison@hhs.gov>; Gorman, Susan (ASPR/SNS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7141173f78da4e519c35756fbbfb2593-Gorman, Sus <spg4@cdc.gov>; Adams, Steven A. (ASPR/SNS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f98462fe8d124743a437c7a80b3f60dd-Adams, Stev <saa1@cdc.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
Subject:	IMPT - HHS Comms requirement for EUA Comms for CQ and HCQ
Date:	2020/03/28 18:33:45
Importance:	High
Priority:	Urgent
Type:	Note

Dear Cicely, Eileen and ASPR Comms.

As you know there is an EUA request that BARDA is about to submit as early as tonight and a nearly final response from the FDA authorizing the EUA. The FDA response is attached.
In this authorization, there are requirements for HHS to communicate the availability of the material in the SNS. FDA will also post notice. See part C of the attached agreement below.

Please advise if HHS wishes to post, ASPR post, or only the posting on the FDA website. Please check in with FDA on the details of the requirement and to coordinate. I wasn't sure who to include from FDA on this.

Thank you,

Linda

C. HHS will ensure that the terms of this EUA are made available to public health authorities through appropriate means.[1] HHS will provide authorized emergency response stakeholders a copy of this letter of authorization and communicate to emergency response stakeholders any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (e.g., Fact Sheets).

F. HHS will inform emergency response stakeholders about the need to have a process in place for performing adverse event monitoring and compliance activities designed to ensure that adverse events and all medication errors associated with the use of the authorized chloroquine phosphate or hydroxychloroquine sulfate are reported to FDA, to the extent practicable given emergency circumstances, as follows: complete the MedWatch FDA Form 3500 online at www.fda.gov/medwatch, by using a postage-paid MedWatch Form 3500 (available at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home), or by calling 1-800-FDA-1088. Submitted reports should state: "use of chloroquine phosphate was under an EUA" or "use of hydroxychloroquine sulfate was under an EUA," as relevant. If and when HHS establishes a process for collecting outcomes data, HHS will inform emergency response stakeholders about such process.

Linda C. Lambert, PhD
Director, Medical Countermeasures Program Support Services
Biomedical Advanced Research and Development Authority (BARDA)
Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-260-1200
Mobile: (b)(6)
email: Linda.Lambert@hhs.gov

Note to contractors: nothing in this e-mail is intended to constitute contractual direction or to impact cost, price, or schedule contained in the contract. If the contractor believes there is an impact, the contractor must disregard that portion of the communication and contact the Contracting Officer for direction.

[1] For example, through hard copy, web posting, and/or mass media.

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Recipient:	Kane, Elleen (OS/ASPR/OEA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=user25dbd6c7 <Elleen.Kane@hhs.gov>; Waters, Cicely (OS/ASPR/OEA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00e638c4ddf64006bcc009e8032dd700-Waters, Cic <Cicely.Waters@hhs.gov>; ASPRMEDIA (OS/ASPR/COO) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=1949c96e6c46444383366c69b467cec1-ASPRMEDIA@h <ASPRMEDIA@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04528b7c91bbd61893975-Houchens, C <Christopher.Houchens@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>; Faison, Tremel (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2bbab0bceb1342fbbedbbcc94deeb80f-Faison, Tre <Tremel.Faison@hhs.gov>; Gorman, Susan (ASPR/SNS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7141173f78da4e519c35756fbbfb2593-Gorman, Sus <spg4@cdc.gov>; Adams, Steven A. (ASPR/SNS) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=f98462fe8d124743a437c7a80b3f60dd-Adams, Stev <saa1@cdc.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>
Sent Date:	2020/03/28 18:33:43
Delivered Date:	2020/03/28 18:33:45
From:	Faison, Tremel (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2BBAB0BCEB1342FBBEDBBCC94DEEB80F-FAISON, TRE <Tremel.Faison@hhs.gov>
To:	Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>
Subject:	FW: Documents
Date:	2020/03/28 16:57:48
Priority:	Normal
Type:	Note

We need signature from Rick by 7:30. I am sending the new LoA to Sil to see if she wants to make any modifications.

From: Corrigan-Curay, Jacqueline <Jacqueline.Corrigan-Curay@fda.hhs.gov>
Sent: Saturday, March 28, 2020 4:S5 PM
To: Faison, Tremel (OS/ASPR/BARDA) <Tremel.Faison@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>
Cc: Beers, Donald (FDA/OC) <Donald.Beers@fda.hhs.gov>; Farley, John (FDA/CDER) <John.Farley@fda.hhs.gov>; Gormley, Andrea (Vincent) (FDA/CDER) <Andrea.Vincent@fda.hhs.gov>; Leissa, Brad G (FDA/CDER) <Brad.Leissa@fda.hhs.gov>; Sadove, Elizabeth (FDA/OC) <Elizabeth.Sadove@fda.hhs.gov>
Subject: Documents

Hi
Thank you for all the helpful feedback this am and the tracked change documents.
Attached please find the documents that we believe are final but we will be doing final proofing
We have left track changes in the LOA so you can see how we addressed some comments
We have left just a few track changes in the FACT Sheets regarding that were later clinical comments
We have moved the tracking of outcomes out of the Mandatory Reporting because we do not yet have a system therefore can't be mandatory
When we have a system we can amend FACT sheets to reflect that

We have been asked by the Commissioner's office to finish this tonight.

Please send us one set of edited documents and your final request letter by 7:30 pm so that we can meet this deadline.

Out plan is to have this signed late tonight or first thing in the am.

Thank you,

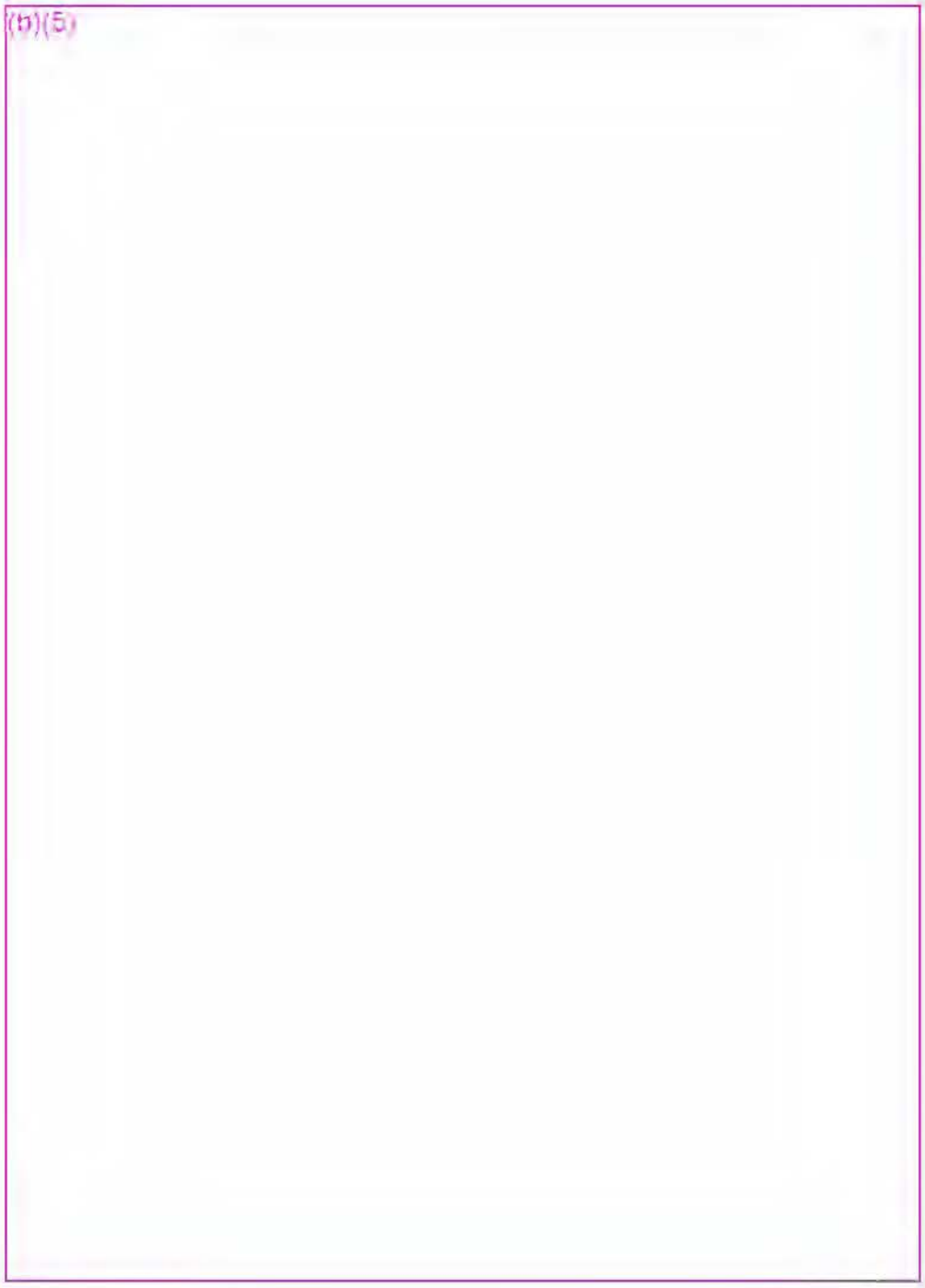
Jacqueline

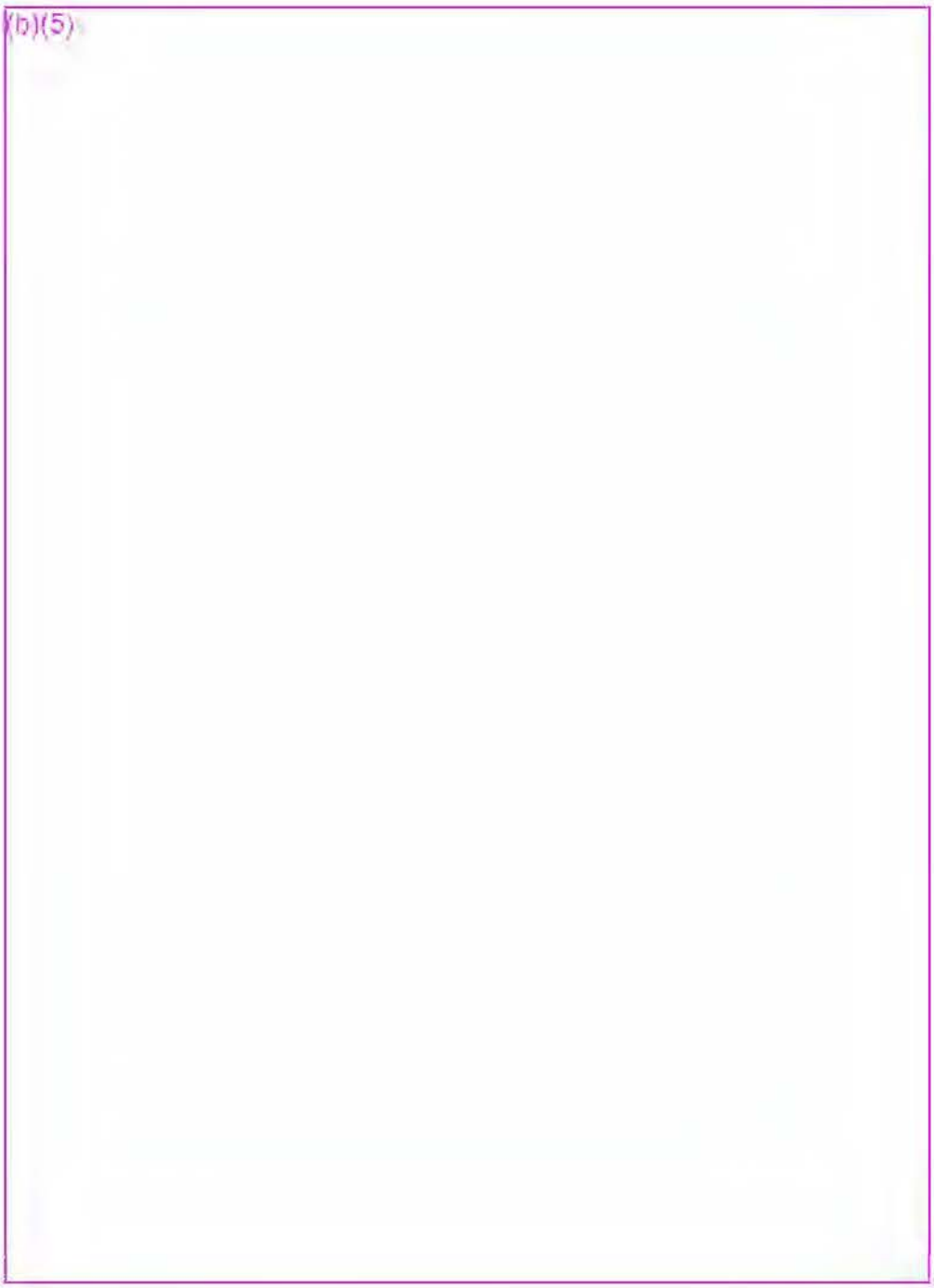
Sender:	Faison, Tremel (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2BBAB0BCEB1342FBBEDBBCC94DEEB80F-FAISON, TRE <Tremel.Faison@hhs.gov>
Recipient:	Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>
Sent Date:	2020/03/28 16:57:46
Delivered Date:	2020/03/28 16:57:48

March XX, 2020

Commented (b)(5)

(b)(5)


(b)(5)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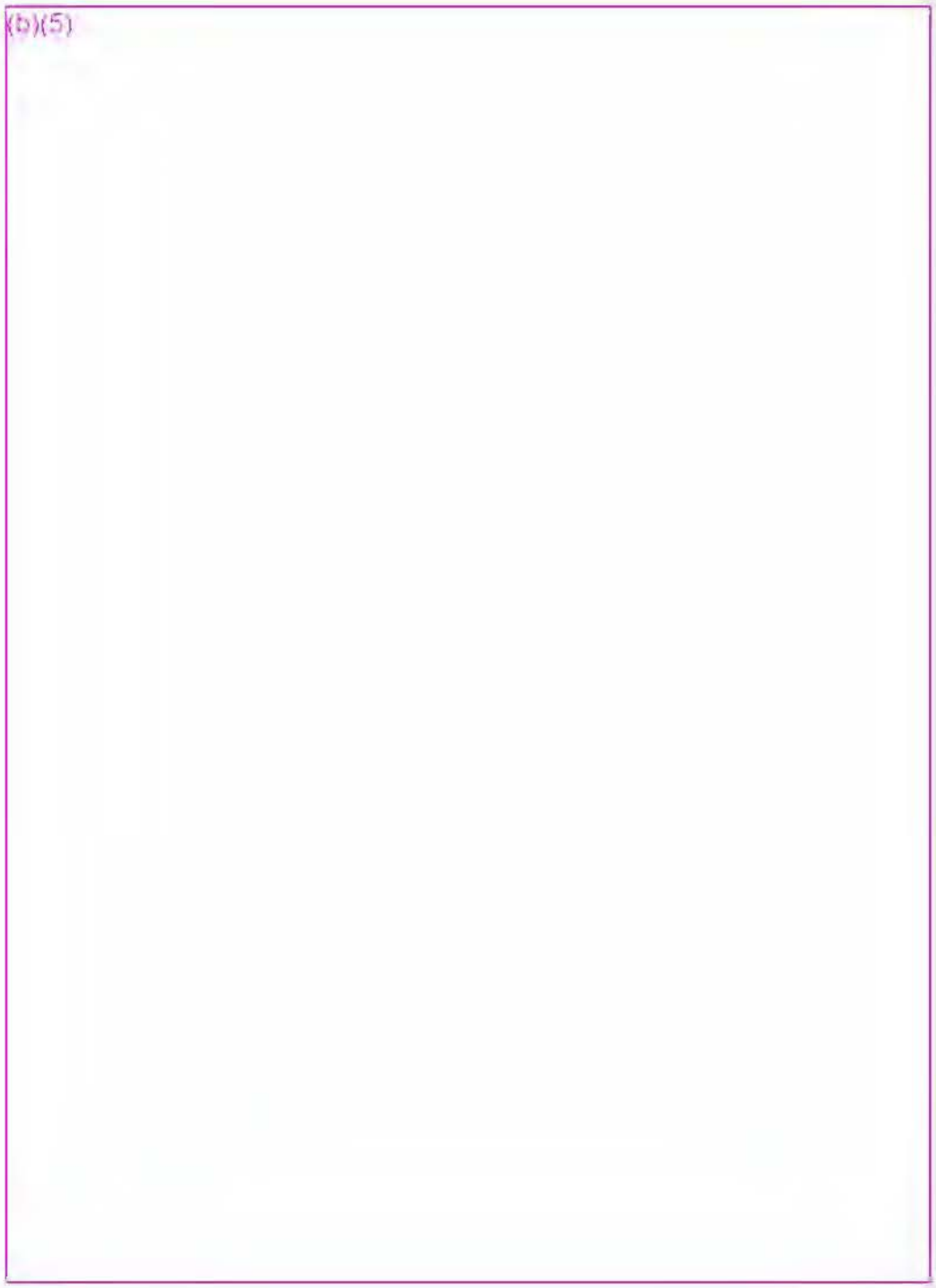
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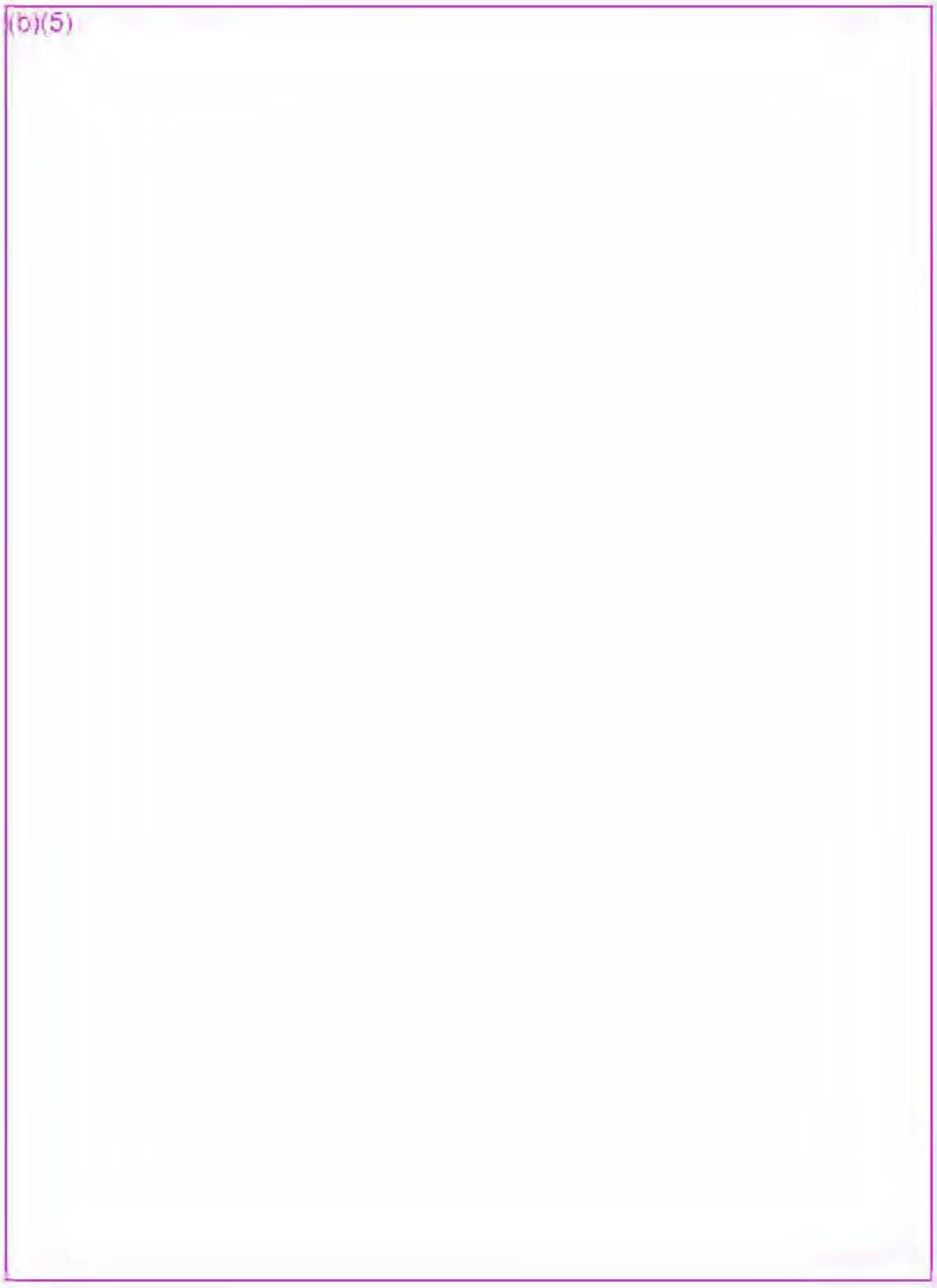
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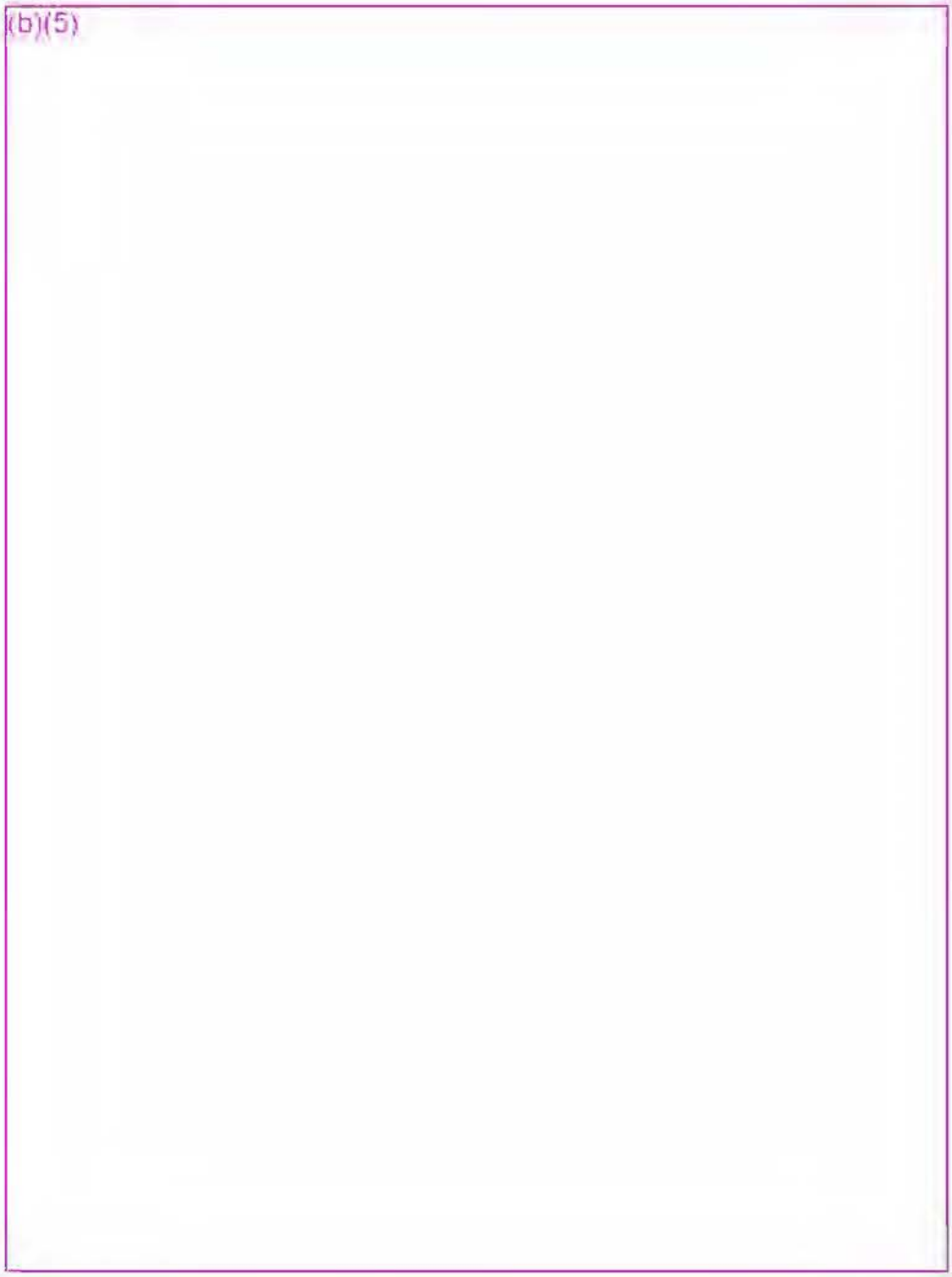

(b)(5)

V. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biologics for prevention and treatment of COVID-19 is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

Enclosures

From:	George Keefe <George.Keefe@tevapharm.com>
To:	Charrow, Robert (HHS/OGC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00531138af454ce3ac0b5885bead345f-Charrow, Ro <Robert.Charrow@hhs.gov>
CC:	Christine Baeder <Christine.Baeder@tevapharm.com>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Michael Brzica <Michael.Brzica@tevapharm.com>
Subject:	RE: FDA PHL Request: hydroxychloroquine API- TEVA
Date:	2020/03/25 11:09:05
Priority:	Normal
Type:	Note

Dear Bob,

It was good to speak with you this morning regarding the prohibition on shipping hydroxychloroquine out of India. As discussed, we are working directly with the Indian Government to allow us to ship our product out of the country. We would appreciate assistance from the US Government in this matter.

Please take a look at the attached letter from the Indian Government. We would like to request a phone meeting to discuss appropriate next steps.

Thanks for your assistance.

Regards,
George

From: Charrow, Robert (HHS/OGC) <Robert.Charrow@hhs.gov>
Sent: Friday, March 20, 2020 1:08 PM
To: Christine Baeder <Christine.Baeder@tevapharm.com>
Cc: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Subject: RE: FDA PHL Request: hydroxychloroquine API- TEVA

We have a call into her and have emailed her. Bob

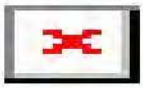
From: Christine Baeder <Christine.Baeder@tevapharm.com>
Sent: Friday, March 20, 2020 1:03 PM
To: Charrow, Robert (HHS/OGC) <Robert.Charrow@hhs.gov>
Cc: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Subject: FW: FDA PHL Request: hydroxychloroquine API- TEVA

Bob,

Thank you for your help. Here is the contact we discussed.

Per our discussion

Best regards,



cid:image001.png@01CB4876.00748C50

Christine Baeder
SVP, Chief Operating Officer US Gx
Tel: 1-215-591-8913 **Cell:** (b)(6)
Christine.Baeder@tevapharm.com https://protect2.fireeye.com/url?k=e054aa7b-bc01a368-e0549b44-0cc47adb5650-d572c0e043a083c1&u=https://protect2.fireeye.com/url?k=4ebf322c-12eb1b07-4ebf0313-0cc47a6d17cc-2354539208ea13ee&u=http://www.tevapharm.com/

From: Heather Conner-Garofalo <Heather.Conner-Garofalo@tevapharm.com>
Sent: Friday, March 20, 2020 12:46 PM
To: Christine Baeder <Christine.Baeder@tevapharm.com>
Cc: Daniel Hoey <Daniel.Hoey@tevapharm.com>; Matthew Roberts <Matthew.Roberts06@tevauk.com>; Chris Lagullo <Chris.Lagullo@tevapharm.com>
Subject: RE: FDA PHL Request: hydroxychloroquine API

Hi Christine,

An e-mail is fine, does not need to be formal. Just that they are asking us to import the API and the person's name and contact information.

If HHS prefers to speak with the FDA officer, her information is as follows:

Tonya O. Corbin
Complionce Officer
DNEI-Philadelphia
Office of Regulatory Affairs
U.S. Food and Drug Administration
Tel: 215-717-3715
Tonya.corbin@fda.hhs.gov

cid:image002.jpg@01D2E03F.8FA9FF50

Officer Corbin is not holding anything up, she is merely responding to my request for guidance as to which ACE-ITDS codes to transmit and what to list in our end use letter.

Thank you,

Heather

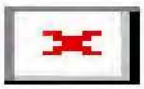
From: Christine Baeder
Sent: Friday, March 20, 2020 12:16 PM
To: Heather Conner-Garofalo
Cc: Daniel Hoey; Matthew Roberts; Chris Lagullo
Subject: RE: FDA PHL Request: hydroxychloroquine API

Heather,

We do not have anything in writing.. If you tell me what you need I will call and ask them to give us a letter. Can you draft what you need and I can forward and ask them to put on the correct letterhead?

Or provide contact information and I can ask HHS to reach out to the appropriate contact at FDA directly?

Best regards,


cid:image001.png@01CB4876.00748C50

Christine Baeder
SVP, Chief Operating Officer US Gx
Tel: 1-215-591-8913 **Cell:** (b)(6)
Christine.Baeder@tevapharm.com https://protect2.fireeye.com/url?k=909dd4d7-ccc8ddc4-909de5e8-0cc47adb5650-b57c0c969332594b&u=https://protect2.fireeye.com/url?k=202f7e4e-7c7b5765-202f4f71-0cc47a6d17cc-2d6428040a2c1204&u=http://www.tevapharm.com/

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Sender:	George Keefe <George.Keefe@tevapharm.com>
Recipient:	Charrow, Robert (HHS/OGC) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=00531138af454ce3ac0b5885bead345f-Charrow, Ro <Robert.Charrow@hhs.gov>; Christine Baeder <Christine.Baeder@tevapharm.com>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric

	<Rick.Bright@hhs.gov>; Michael Brzica <Michael.Brzica@tevapharm.com>
Sent Date:	2020/03/25 11:08:40
Delivered Date:	2020/03/25 11:09:05

From:	Lambert, Linda (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CE6824B6A92A4A4E893EA7B54E17EB3C-LAMBERT, LI <Linda.Lambert@hhs.gov>
To:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
CC:	Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>
Subject:	Request for BARDA help with DLG | International MCM Access and population prioritization for MCM
Date:	2020/04/14 11:43:51
Priority:	Normal
Type:	Note

Rick and Gary
SPPR is asking for a BARDA rep to help work up a DLG on population prioritization for CQ/HCQ and possibly broader.

I'll let them know that we can't staff this because of our response mode today. **Holler if otherwise.**

Linda

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Tuesday, April 14, 2020 11:26 AM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>; DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Subject: RE: DLG | International MCM Access

Thanks, Linda. We'd be interested to have whoever at BARDA would be appropriate to discuss how to frame the DLG discussion on population prioritization decisions that would include international access to MCMs, especially when they are limited. Who would be the right person?

From: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Sent: Tuesday, April 14, 2020 11:17 AM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel

(HHS/OS/OGA) <Rachel.Wood@hhs.gov>; DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi All,
Thank you for the invite. I do not think I can contribute to population prioritization. My expertise is micro and product development with a minor in human resources/HR since joining ASPR.
L

From: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Sent: Tuesday, April 14, 2020 11:09 AM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>; DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Subject: RE: DLG | International MCM Access

I could meet between 11:00 and 12:00 tomorrow. We'll need a rep from the DLG team also. Dan

---

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Tuesday, April 14, 2020 11:05 AM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Thank you, Dan. Could we please schedule a time with you and Linda (and whoever else needs to be on the call) to discuss bringing the issue of population prioritization that includes the international piece to the DLG? Dan and Linda, what is your availability tomorrow between 11-2? Thank you both!

From: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Sent: Tuesday, April 14, 2020 9:33 AM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Thanks all. Let us know if/when you want to consider a DLG on this topic. As noted, it might be similar to other DLGs we've had on related topics. I'm happy to discuss. Dan

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Tuesday, April 14, 2020 8:31 AM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi Linda,

Thank you very much for the quick turnaround on this. This is helpful!

All the best,

Ana

From: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Sent: Monday, April 13, 2020 7:46 PM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Cc: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi Ana,

We aren't aware of any ongoing discussions in BARDA on this as it's a policy issue. However, a suggestion came back. Should Remdesivir demonstrate efficacy it was suggested that a policy position on Remdesivir could be considered for COVID-19 the same way that it was during the 2 Ebola outbreaks.

Thank you all again. We appreciate SPPR checking in with us on this.

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Monday, April 13, 2020 4:21 PM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

+ Rachel Wood

From: Ayala, Ana (OS/ASPR/SPPR)
Sent: Monday, April 13, 2020 4:20 PM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Subject: FW: DLG | International MCM Access

Hi Linda,

Dan Dodgen (copied here) suggested that we reach out to you as one of the starting points as we look into the possibility of having an HHS-internal discussion within the DLG on how international access to COVID-19 MCMs should be handled and balancing that with domestic needs. Some of us have started considering the various complications that could arise as MCMs like Remdesivir become available but in limited numbers, at which point we expect that international stakeholders like WHO and other foreign governments will reach out. Has BARDA started to have conversations internally (or externally with stakeholders) on this issue? We would be interested to hear what BARDA is thinking on the issue.

Many thanks in advance,

Ana

Ana S. Ayala, J.D., LL.M.
Senior Global Health Officer
Office of Global Affairs
U.S. Department of Health and Human Services (HHS)
o: (202) 205-5894 | **m:** (b)(6)
ana.ayala@hhs.gov

From: Ayala, Ana (OS/ASPR/SPPR)
Sent: Monday, April 13, 2020 3:04 PM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>; Moudy, Robin (OS/ASPR/SPPR) <Robin.Moudy@hhs.gov>
Subject: RE: DLG | International MCM Access

Thank you, Dan. We haven't had discussions with BARDA on international access to Remdesivir yet. We'll reach out to Linda Lambert to see whether they've begun considering the issue. Regardless, it would be good to have the HHS-internal discussion within DLG to start addressing international access to MCMs in general (does not need to be limited to Remdisivir). Of course, it would make sense to have it as part of a discussion on how various populations will be prioritized when amounts are limited—don't think the DLG could consider the international piece without addressing this first.

If you could please share with us the DLG paper, that would be great. Since Robin and Ruvani helped draft the paper at the early stages, we did not hear on further developments. We'd be particularly interested in how ASPR plans to move forward. Thanks in advance!

Ana

From: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Sent: Monday, April 13, 2020 2:26 PM
To: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: RE: DLG | International MCM Access

Hi Ana, Thanks for your message. As you know, we are currently finalizing a DLG paper regarding the use of HHS-held chloroquine and hydroxychloroquine in international clinical trials. There may be content relevant to your question in the paper, which we hope to finalize today or tomorrow.

Have you spoken with BARDA about the Remdesivir question yet? They have been so engaged in the Remdesivir trials that they may have already given some thought to this issue. I would start with Linda Lambert.

That said, this could be a potential DLG topic if we need broader HHS input and/or consensus. Let's see how BARDA responds. Dan

---

From: Ayala, Ana (OS/ASPR/SPPR) <Ana.Ayala@hhs.gov>
Sent: Monday, April 13, 2020 2:06 PM
To: Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>
Cc: Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Chandrasekera, Ruvani (OS/ASPR/SPPR) <Ruvani.Chandrasekera@hhs.gov>; Weinberger, Collin (OS/OGA) <Collin.Weinberger@hhs.gov>; Wood, Rachel (HHS/OS/OGA) <Rachel.Wood@hhs.gov>
Subject: DLG | International MCM Access

Hi Dan,

Hope you are doing well. We are reaching out with respect to an issue that has begun to come up and which we expect will continue to grow in significance. With advocacy for Remdesivir increasing as a hopeful COVID-19 MCM and considering that the DLG is the coordinating body for high-level policy decisions, we would like to inquire about the possibility of starting an internal HHS conversation about the issue of international access to Remdesivir and our approach with respect to WHO inquiries about

accessing it. Has the DLG started discussions on prioritizing populations with respect to Remdesivir or other hopeful MCM candidates? This may be the starting point to consider the potential international aspects of what may be soon coming down the pike.

Many thanks!

Ana

Ana S. Ayala, J.D., LL.M.
Senior Global Health Officer
Office of Global Affairs
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (DHHS)
o: (202) 205-5894 | m: (b)(6)
ana.ayala@hhs.gov

Sender:	Lambert, Linda (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=CE6824B6A92A4A4E893EA7B54E17EB3C-LAMBERT, LI <Linda.Lambert@hhs.gov>
Recipient:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>
Sent Date:	2020/04/14 11:43:50
Delivered Date:	2020/04/14 11:43:51

From:	Disbrow, Gary (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA <Gary.Disbrow@hhs.gov>
To:	Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>
CC:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	RE: COMMERCIAL CONFIDENTIAL INFORMATION
Date:	2020/04/05 07:56:51
Priority:	Normal
Type:	Note

Bob,

They will submit on Monday. They indicated they have safe to proceed from IRB. They indicated an IND was not necessary but they have safe to proceed from FDA. Perhaps it simply states that an IND is not required since it is an OTC drug. I have no idea.

It should be able to efficiently and rigorously compare hydroxychloroquine + SOC vs SOC (historic control data @ Northwell), hydroxychloroquine + famotidine IV + SOC vs historic SOC, and hydroxy vs hydroxy + famotodine. All double blinded and properly randomized. 1200 subjects in two groups of 600 in active treatment compared to the historic control group. Hospitalized as moderate COVID19 without lymphopenia. Clinical endpoint as primary.

Gary L. Disbrow Ph.D.
Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-260-0899
Mobile: (b)(6)
Fax: 202-205-0873
email: Gary.Disbrow@HHS.gov

Note to contractors: nothing in this e-mail is intended to constitute contractual direction or to impact cost, price, or schedule contained in the contract. If the contractor believes there is an impact, the contractor must disregard that portion of the communication and contact the Contracting Officer for direction

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From: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>
Sent: Sunday, April 5, 2020 7:51 AM
To: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Subject: Re: COMMERCIAL CONFIDENTIAL INFORMATION

Thanks Gary. Rick wants bullets from me today for a 4 pm meeting. Currently I can only say it's an h2 blocker and that histamine release by mast cells has been postulated to contribute to the pulmonary inflammation associated with SARS-CoV-2 infection. No data are available to substantiate this.

On Apr 5, 2020, at 4:05 AM, Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>wrote:

Bob,

I don't want to get you involved. Please see below.

Gary L. Disbrow Ph.D.
Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-260-0899
Mobile: (b)(6)
Fax: 202-205-0873
email: Gary.Disbrow@HHS.gov

Note to contractors: nothing in this e-mail is intended to constitute contractual direction or to impact cost, price, or schedule contained in the contract. If the contractor believes there is an impact, the contractor must disregard that portion of the communication and contact the Contracting Officer for direction

From: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Sent: Sunday, April 5, 2020 4:04 AM
To: KJTracey@northwell.edu; (b)(6)
Cc: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>
Subject: COMMERCIAL CONFIDENTIAL INFORMATION

Dr. Malone,

In your submission, please provide references that would indicated famotidine as a potential therapeutic for COVID19. Everyone understands it is a H2 blocker and can be provided to individuals with anaphylaxis in combination with epinephrine but alone is not sufficient for airway/lung improvement. Simple explanation and reference would assist in the review. Please let me know when you have submitted as this has been identified as a priority by the ASPR.

This email does not indicate a decision on potential funding.

Regards

Gary

Gary L. Disbrow Ph.D.
Deputy Assistant Secretary
Director, Medical Countermeasure Programs
Biomedical Advanced Research and Development Authority
BARDA
Assistant Secretary for Preparedness and Response ASPR
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201
Office: 202-260-0899
Mobile (b)(6)
Fax: 202-205-0873
email: Gary.Disbrow@HHS.gov

Sender:	Disbrow, Gary (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=0FD5845DEFDA4DC0BB45F8FAC629CF09-DISBROW, GA <Gary.Disbrow@hhs.gov>
Recipient:	Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Sent Date:	2020/04/05 07:56:50
Delivered Date:	2020/04/05 07:56:51

From:	Faison, Tremel (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2BBAB0BCEB1342FBBEDBBCC94DEEB80F-FAISON, TRE <Tremel.Faison@hhs.gov>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>
CC:	Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>
Subject:	RE: Nationwide Access Plan
Date:	2020/03/26 09:07:47
Priority:	Normal
Type:	Note

Good morning Rick,

FDA is willing to write the EUA. However there must be a Sponsor who requests the EUA from FDA. I contacted FDA OCET to confirm this.

So, BARDA will be the sponsor of this EUA?

Tremel

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Thursday, March 26, 2020 8:57 AM
To: Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>
Cc: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Faison, Tremel (OS/ASPR/BARDA) <Tremel.Faison@hhs.gov>
Subject: Re: Nationwide Access Plan

See highlighted section below. The said no. The SNS should be the one to distribute the drug.

Please feel free to engage the partners for clarification.

From: Linda Lambert <Linda.Lambert@hhs.gov>
Date: Thursday, March 26, 2020 at 8:32 AM
To: "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>
Cc: Robert Walker <Robert.Walker@hhs.gov>, Tremel Faison <Tremel.Faison@hhs.gov>
Subject: Re: Nationwide Access Plan

Got it Rick.

Did you talk with CDC about their willingness to sponsor the EUA?

We can use PPD for support but critical to know if CDC will sponsor?

Sent from my iPhone

On Mar 26, 2020, at 8:06 AM, Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>wrote:

Bob and Linda, I realize this is a tiger, please reduce this group as you find necessary, manageable size to move this forward, but keep every agency and group represented throughout the process.

Linda, you are the DAS level in the lead, please feel empowered to execute this action.

Bob, it is critical to have a group meeting today to align the SNS and Hamel on the supply portion of this trial. SNS will be responsible for receiving the drug and distribution perhaps? Or will the drug go to your CRO and they manage the distribution?

CDC – Shuchat has said they will not write EUA, but I think FDA is writing EUA. CDC says they failed to manage the prior EUA and has no ability or expertise to do so. Suggested that the CRO do this part. They can make available some CDC staff from the peramivir experience to assist in the planning stage to contribute lessons learned.

Can PPD take this on if FDA write EUA and SNS receives and distributes the drug?

IT IS CRITICAL THAT EVERY STEP IS PLANNED IN FULL PARTICIPATION AND VISIBILTY OF EACH OF THE INTERAGENCY COLLEAGUES AND PARTNERS. While many are trying to wash their hands of this, we do not want any to say they were unaware and did not have a chance for input, feedback, pushback, etc. Please get concurrence from their highest level representative. Linda, please ensure this happens.

Thank you both and your teams for so much hard work and leadership. Rick

---

From: Joseph Hamel <Joseph.Hamel@hhs.gov>
Date: Thursday, March 26, 2020 at 7:53 AM
To: "Amin, Stacy (FDA/OC)" <Stacy.Amin@fda.hhs.gov>
Cc: "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>, Robert Walker <Robert.Walker@hhs.gov>, Tremel Faison <Tremel.Faison@hhs.gov>, "Farley, John (FDA/CDER)" <John.Farley@fda.hhs.gov>, Linda Lambert <Linda.Lambert@hhs.gov>, Christine Oshansky <Christine.Oshansky@hhs.gov>, Gary Disbrow <Gary.Disbrow@hhs.gov>, Hilary Marston <hilary.marston@nih.gov>, Cliff Lane <clane@niaid.nih.gov>, Anita Patel <bop1@cdc.gov>, Timothy Uyeki <tmu0@cdc.gov>, "Hepburn, Matthew J CIV USARMY DOD JPEO CBRND (USA)" <(b)(6)>, Debra Birnkrant

<Debra.Birnkrant@fda.hhs.gov>, John Beigel <jbeigel@niaid.nih.gov>, Elizabeth Higgs <ehiggs@niaid.nih.gov>, "Sherman, Susan (HHS/OGC)" <Susan.Sherman@HHS.GOV>, "Harper, Victor (OS/ASPR/ORM)" <Victor.Harper@hhs.gov>, "Adams, Steven A. (ASPR/SNS)" <saa1@cdc.gov>, Janet Woodcock <Janet.Woodcock@fda.hhs.gov>, Robert Johnson <Robert.Johnson@hhs.gov>, "Guram, Jeet (FDA/OC)" <Jeet.Guram@fda.hhs.gov>, "Franklin, Joseph (FDA/OC)" <Joseph.Franklin@fda.hhs.gov>, "Charrow, Robert (HHS/OGC)" <Robert.Charrow@hhs.gov>
Subject: Re: Nationwide Access Plan

That is consistent. We should also all talk about patient access and our consolidated strategy to meet surge demands. Thank you for starting this topic!

Strategic Innovation and Emerging Technology Manager
Assistant Secretary for Preparedness and Response
Office: 202-969-3852
Cell: (b)(6)

On Mar 25, 2020, at 10:06 PM, Amin, Stacy <Stacy.Amin@fda.hhs.gov>wrote:

Renaming this email thread since we are no longer talking about an IND.

FDA needs to please have Jeet Guram and Joe Franklin added to all calls and emails about chloroquine and hydroxychloroquine. They will loop the appropriate FDA folks.

We have an urgent question. CDER is working on an EUA for the Bayer chloroquine donation that will take several days to complete. FDA is not currently planning to work on the Sandoz hydroxychloroquine EUA until after the Bayer EUA. Is that consistent with ASPR's needs?

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Wednesday, March 25, 2020 6:00 PM
To: Amin, Stacy <Stacy.Amin@fda.hhs.gov>; Walker, Robert (OS) <Robert.Walker@hhs.gov>; Faison, Tremel (OS) <Tremel.Faison@hhs.gov>; Farley, John <John.Farley@fda.hhs.gov>; Lambert, Linda (OS) <Linda.Lambert@hhs.gov>; Oshansky, Christine (OS) <Christine.Oshansky@hhs.gov>; Disbrow, Gary (OS) <Gary.Disbrow@hhs.gov>; Marston, Hilary D (NIH) <hilary.marston@nih.gov>; Lane, Henry C (NIH) <clane@niaid.nih.gov>; Patel, Anita (CDC) <bop1@cdc.gov>; Uyeki, Timothy M (CDC) <tmu0@cdc.gov>; Hepburn, Matthew J CIV USARMY DOD JPEO CBRND (USA) <(b)(6)>; Birnkrant, Debra B <Debra.Birnkrant@fda.hhs.gov>; Beigel, John H (NIH) <jbeigel@niaid.nih.gov>; Higgs, Elizabeth S (NIH) <ehiggs@niaid.nih.gov>; Sherman, Susan (OS) <Susan.Sherman@HHS.GOV>; Harper, Victor G (OS) <Victor.Harper@hhs.gov>; Adams, Steven A (CDC) <saa1@cdc.gov>; Woodcock, Janet <Janet.Woodcock@fda.hhs.gov>; Johnson, Robert (OS) <Robert.Johnson@hhs.gov>; Hamel, Joseph (OS) <Joseph.Hamel@hhs.gov>
Subject: Re: URGENT Questions on planned study

Apologies for the resend, I accidentally omitted Joe Hamel. He has a critical role. Thanks. Rick

FOUO, Confidential, Pre-Decisional

Dear All,

I am following up on our HHS task of implementing a "nationwide access plan" for chloroquine and/or hydroxychloroquine. This project has been discussed in multiple settings with multiple members of the larger group. As we proceed towards implementation, it is critical to keep the full agency visibility on the project to ensure each plays a role in execution. I have included HHS, ASPR/IO, ASPR SNS, NIH/NIAID, CDC, ASPR/BARDA, FDA/OGC, FDA/OC, FDA/CDER, HHS/OGC. The distribution above can be reduced to the single agency representative once all roles are finalized.

We learned today from our FDA colleagues that plans are progressing quickly to move forward with an EUA (not an IND). The FDA will write the EUA(s). The following specific items will need to be fully understood and appropriate actions taken by our agency teams as indicated. Please update any errors or incorrect assumptions.

- First, question (focus on hydroxychloroquine only or also include chloroquine)?
- Chloroquine (Bayer donation)
- The current plan is to make chloroquine available under an Emergency Use Authorization.
- The indicated population remains to be determined. The MCM Task Force **clinical trial working group** will provide input into that decision.
- As has historically been the HHS approach for EUAs, **CDC will lead** for implementation of the EUA effort and distribution of product in collaboration with SNS.
- This will be an initial small-scale roll-out/pilot as discussed on the interagency call on March 23rd, in a limited number of locations.
- All questions about drug supply and other product specific concerns are directed to Joe Hamel in the ASPR Immediate Office.
- All product will be received, stored and distributed by the ASPR/SNS.

- Hydroxychloroquine (Sandoz/Novartis donation)
- FDA is actively considering making hydroxychloroquine available under an EUA.

- To better inform this decision, information is needed by FDA about drug supply to ensure that appropriate doses are set aside for clinical trials.
- As above, should the final decision of the HHS be to proceed with an EUA, the interagency team will look to CDC to lead the EUA implementation in collaboration with SNS.
- All questions about drug supply and other product specific concerns are directed to Joe Hamel in the ASPR Immediate Office.

  All product will be received, stored and distributed by the ASPR/SNS.

  ORACLE: We need to understand the full scope and nature of the Oracle donation and have a POC at Oracle to coordinate this portion of the plan. Who has been the HHS POC for Oracle to date?

  Donations: Are all donations complete? Oracle? Bayer? Sandoz/Novartis?
- Dr. Bob Walker in BARDA is coordinating the group.

Thank you all for your critical and urgent contributions to these collaborative efforts.

Rick

From: "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>
Date: Monday, March 23, 2020 at 9:09 PM
To: "Amin, Stacy (FDA/OC)" <Stacy.Amin@fda.hhs.gov>
Cc: Janet Woodcock <Janet.Woodcock@fda.hhs.gov>, Robert Johnson <Robert.Johnson@hhs.gov>, Robert Walker <Robert.Walker@hhs.gov>, Tremel Faison <Tremel.Faison@hhs.gov>, "Farley, John (FDA/CDER)" <John.Farley@fda.hhs.gov>, Linda Lambert <Linda.Lambert@hhs.gov>, Christine Oshansky <Christine.Oshansky@hhs.gov>, Gary Disbrow <Gary.Disbrow@hhs.gov>, Hilary Marston <hilary.marston@nih.gov>, Cliff Lane <clane@niaid.nih.gov>, Anita Patel <bop1@cdc.gov>, Timothy Uyeki <tmu0@cdc.gov>, "Hepburn, Matthew J CIV USARMY DOD JPEO CBRND (USA)" <(b)(6) Debra Birnkrant <Debra.Birnkrant@fda.hhs.gov>, John Beigel <jbeigel@niaid.nih.gov>, Elizabeth Higgs <ehiggs@niaid.nih.gov>, "Sherman, Susan (HHS/OGC)" <Susan.Sherman@HHS.GOV>
Subject: URGENT Questions on planned study

Hi Stacy,

I hope that you are doing well, given the extremely busy pace that everyone is working. I hope that you are able to assist us with an urgent matter.

HHS has been tasked to conduct what we understand to be a nationwide emergency access IND for Chloroquine or hydroxychloroquine. The HHS COVID19 clinical and regulatory teams urgently need to talk with you to understand the information that you have about this study and a potential combination with an experimental database system from Oracle.

The details available enable us to proceed are very sketchy and the directive is to move quickly. We understand that you might have helpful information from various conversations you have had with Oracle, the drug supplier and other entities planning the trial. In order to coordinate this USG/HHS-lead study, it will be very helpful if you can update us on any background information, either by email or a conference call.

Dr. Bob Walker is copied with the HHS team above. He can assist in coordinating a call at your earliest convenience.

Thank you for taking the time to assist in clarifying this task and a path forward.

Rick
Rick A. Bright, PhD
Director, BARDA
Deputy Assistant Secretary for Preparedness and Response
Office of the Assistant Secretary for Preparedness and Response
US Department of Health and Human Services

Sender:	Faison, Tremel (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=2BBAB0BCEB1342FBBEDBBCC94DEEB80F-FAISON, TRE <Tremel.Faison@hhs.gov>
Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>; Walker, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7a02e128c60f4a7195532a1545af9556-Walker, Rob <Robert.Walker@hhs.gov>
Sent Date:	2020/03/26 09:06:52
Delivered Date:	2020/03/26 09:07:47
Message Flags:	Unread

From:	Bartrum, John (OS/ASPR) (CTR) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=FB2CC9052221421C8D5B7FD480F25BBE-BARTRUM, JO <John.Bartrum@hhs.gov>
To:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	RE: Letter to FDA to request EUA for chloroquine and hydroxycloroquine - for signature
Date:	2020/03/28 20:35:51
Priority:	Normal
Type:	Note

No problem.

I am glad Joe saw the item.

I sent Bob a note asking to standby. He just departed so may well be driving home. I think Joe and you team are about final. Thus, I told them once they agree to send to Bob.
John

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Saturday, March 28, 2020 8:29 PM
To: Bartrum, John (OS/ASPR) (CTR) <John.Bartrum@hhs.gov>
Subject: Re: Letter to FDA to request EUA for chloroquine and hydroxycloroquine - for signature

Thank you John. Glad you caught it. I knew the right thing to do was get final eyes on this before ASPR approved.

When you get it back please let him know they are hoping it gets approved and signed tonight. We are on standby. Many thanks sir. Rick.

On Mar 28, 2020, at 8:26 PM, Bartrum, John (OS/ASPR) (CTR) <John.Bartrum@hhs.gov>wrote:

Tremel &Joe – when you have the package coordinated and final – please resend as requested.

Thanks – John

Note – I dropped off Dr. Kadlec until it is completed and ready for his review.

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Saturday, March 28, 2020 8:14 PM

To: Bartrum, John (OS/ASPR) (CTR) <John.Bartrum@hhs.gov>
Cc: Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; Shuy, Bryan (OS/ASPR/IO) <Bryan.Shuy@hhs.gov>; Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>; Hayes, Jonathan (OS/ASPR/IO) <Jonathan.Hayes@hhs.gov>; Faison, Tremel (OS/ASPR/BARDA) <Tremel.Faison@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Sherman, Susan (HHS/OGC) <Susan.Sherman@HHS.GOV>
Subject: Re: Letter to FDA to request EUA for chloroquine and hydroxycloroquine - for signature

John, I'm connecting you and Joe to Tremel and Linda who've worked on the document and Susan who's reviewing for legal.

Please work with them to address any questions.

Thanks. Rick.

On Mar 28, 2020, at 8:09 PM, Bartrum, John (OS/ASPR) (CTR) <John.Bartrum@hhs.gov>wrote:

Rick,

My understanding is this document may not include a couple key edits requested by Joe that may impact our procurement option.

Please work with Joe to resolve and send a summary the changes with the revised document for Dr. Kadlec's review.

Thanks,
John

John J. Bartrum, BG, USAF, MSC
COVID-19 ESF-8 (Med) Deputy Commander
Rm 8NW-2007, Cell (b)(6)

From: Rick Bright <Rick.Bright@hhs.gov>
Sent: Saturday, March 28, 2020 7:43 PM
To: Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>
Cc: Yeskey, Kevin (OS/ASPR/IO) <Kevin.Yeskey@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Shuy, Bryan (OS/ASPR/IO) <Bryan.Shuy@hhs.gov>; Faison, Tremel (OS/ASPR/BARDA) <Tremel.Faison@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>; Redd, John (OS/ASPR/SPPR) <John.Redd@hhs.gov>; Hamel, Joseph (OS/ASPR/IO) <Joseph.Hamel@hhs.gov>;

Harper, Victor (OS/ASPR/ORM) <Victor.Harper@hhs.gov>; Bartrum, John (OS/ASPR) (CTR) <John.Bartrum@hhs.gov>; Sherman, Susan (HHS/OGC) <Susan.Sherman@HHS.GOV>
Subject: Re: Letter to FDA to request EUA for chloroquine and hydroxycloroquine - for signature

Dr. Kadlec,

As directed by the department, HHS agencies CDC, ASPR, FDA, BARDA, and NIH have worked rapidly to develop an EUA protocol for hydroxychloroquine and chloroquine per the direction.

The attached letter has been drafted by HHS and OGC and is ready for signature and transmission.

I seek your final review and concurrence to sign and submit. Once received, this will be transmitted to FDA and they will submit a response letter.

I await your concurrence to proceed.

Thank you. Rick

On Mar 28, 2020, at 7:31 PM, Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>wrote:

Dear Rick,
Attached is the EUA request letter for the EUA. FDA will review and issue a letter of acceptance for the EUA.
The request for emergency use of chloroquine and hydroxychloroquine is based on collaborative, USG-interagency effort to rapidly respond to this continuously evolving public health emergency.
Please review, sign and send to Tremel Faison who will transmit this to the FDA.
Thank you,
Linda

Linda C. Lambert, PhD
Director, Medical Countermeasures Program Support Services
Biomedical Advanced Research and Development Authority (BARDA)
Assistant Secretary for Preparedness and Response (ASPR)
Department of Health and Human Services
330 Independence Avenue, S.W. Room 640 G
Washington, D.C. 20201

Office: 202-260-1200
Mobile: (b)(6)
email: Linda.Lambert@hhs.gov

<CQ and HCQ Emergency Use Request Letter request to FDA_final.pdf>

Sender:	Bartrum, John (OS/ASPR) (CTR) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=FB2CC9052221421C8D5B7FD480F25BBE-BARTRUM, JO <John.Bartrum@hhs.gov>
Recipient:	Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Sent Date:	2020/03/28 20:35:50
Delivered Date:	2020/03/28 20:35:51

BARDA COVID-19 Acquisitions Report - Brief Report - Active

2020-04-20 9:09:54 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Acquisition Vehicle	Obligated Amount	Date of Action	Award or Reprogramming	Project Status
(b)(4); (b)(5)							

BARDA COVID-19 Acquisitions Report - Brief Report - Pending

2020-04-20 9:09:54 -04:00
Last Refreshed

Organization Name	Project Name	Product Category	Acquisition Vehicle	Obligated Amount	Date of Action	Award or Reprogramming	Project Status
(b)(4); (b)(5)							

BARDA COVID-19 Acquisitions Report - Obligated and Active

2020-04-20 9:09:54 -04:00
Last Refreshed

(b)(4); (b)(5)

BARDA COVID-19 Acquisitions Report - Appropriation vs Obligation

2020-04-20 9:09:54 -04:00
Last Refreshed

(b)(4); (b)(5)

BARDA COVID-19 Acquisitions Report - Location Information

2020-04-20 9:09:54 -04:00
Last Refreshed

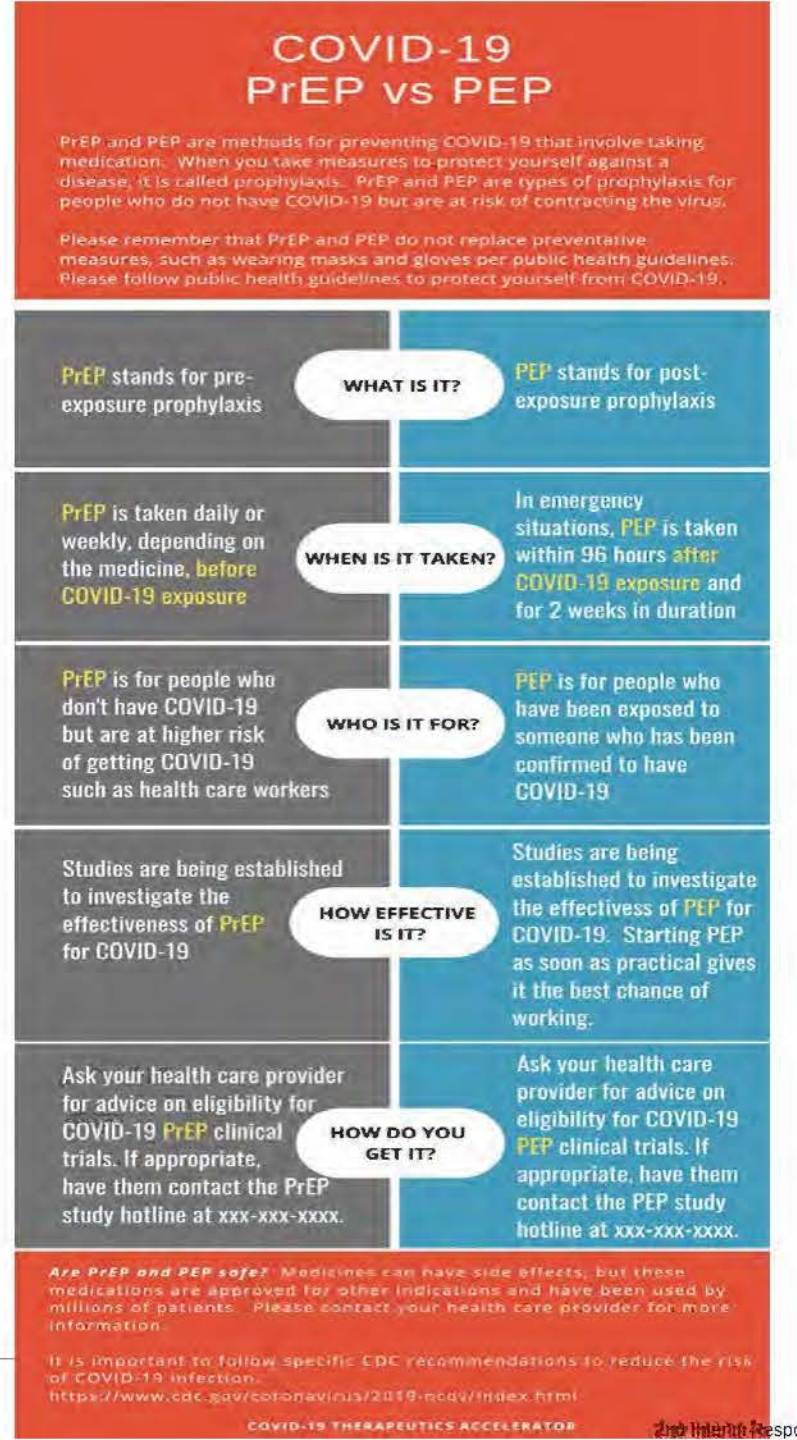
Organization Name	Project Name	Product Category	Obligated Amount	Date of Action	City	State / Province	Country
(b)(4); (b)(5)							

PREP VS PEP USES

- **Post exposure prophylaxis (PEP)** is for health care workers with a documented unprotected exposure, either due to ineffective triage of a suspect case or lack of proper PPE. It is also a strategy for family members care for an index case in a home setting to prevent spread
    - it requires high initial dosing to achieve protective drug levels, and sustained doing only through the incubation period of 14 days

-

-- **Pre-exposure prophylaxis (PrEP)** is only for health care workers likely to be exposed but for whom PPE is not likely available or inadequate for protection
    - not quite the same urgency to get to therapeutic levels, so tolerability is primary focus
    - delivered during the entire period at risk (studies are targeting 90 days)



REPURPOSED DRUGS DISCUSSED FOR SARS-COV-2 HEALTH CARE WORKER PROPHYLAXIS

1. Options: Chloroquine and Hydroxychloroquine
   a) Based off malaria chemoprophylaxis and chronic antirheumatic uses
   b) Dosing ranges
      i. High: loading dose followed by daily dosing for 3 months
      ii. Mid: loading dose followed by bi weekly dosing for 3 months
      iii. Low: loading dose followed by weekly dosing for 3 months

2. Lopinavir/ritonavir:
   a) Based off use in HIV ART
   b) Dosing ranges:
      i. High: 800/200mg given twice daily for 3 months
      ii. Low: 800/200mg given daily for 3 months

POST-EXPOSURE PROPHYLAXIS (PEP)

PEP STUDY: UW (BMGF)

A randomized, single-blind study of tolerability, safety and preventive efficacy of post exposure prophylaxis in adults exposed to COVID-19

Summary

PI: Ruanne Barnabas, UW
Multicenter: Yes
Locations: UW, NYU, 2 others in US

Status: March 17, 2020
In IRB review

Start Date: 24 March 2020
End date: ~3 months

Funding/ Next Steps

COVID-19 Therapeutics Accelerator, grant in process

Documents

Platform protocol to allow testing of alternate agents

Study Aim

To determine the efficacy of hydroxychloroquine administered at the accepted dosing schedules to prevent incident SARS-CoV-2 infection among close adult contacts of the confirmed index persons with COVID-19

Study Synopsis

Design: A single blind randomized by household1:1 to receive hydroxychloroquine versus ascorbic acid
Study Size: 2000 adults; assume 6% attack rate and 50% protection
Study Population: Men and women aged 18-80 years without signs or symptoms of COVID-19 disease who have been exposed to a person with SARS-CoV-2 infection with 4 days. HCW and family members.
Study Drug: Hydroxychloroquine (400 mg orally daily for three days, then 200 mg orally daily for an additional 11 days, to complete 14 days) versus ascorbic acid given on same schedule.
Primary outcome: PCR-confirmed SARS-CoV-2 infection from self-collected samples collected daily at baseline and through 14 days and again 1 week later.

Inclusion: Male or female $\geq$18 and $\leq$ 80 yrs with potential exposure to COVID-19 (health worker, family member)
Exclusions: Hypersensitivity to CQ, potential DDi; potential QCt elongation

PEP STUDY: BARCELONA, SPAIN

Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: a Cluster Randomized Clinical Trial (PEP CoV-2 Study)

Summary

PI: Oriol Mitja, Associate Professor
Infectious Diseases and Global Health
Hospital
Universitari Germans Trias I Pujol,
Badalona, Barcelona, Spain
Multicenter: No
Location(s): Catalonia, Spain
Status: ongoing; v11
Start Date: March 16, 2020
End date: April 30, 2020

Funding/ Next Steps

Local funding
Seeking EU funders for more sites

Documents

ClinicalTrials: NCT04304053
Full protocol here

Study Aims

- To evaluate the effectiveness to reduce transmissibility and disease progression of antiviral treatment of all who are found to be infected and chemoprophylaxis of close contacts assessed by secondary attack rate of COVID-19 among contacts in the control and experimental arm.

Study Synopsis

Design: Community based targeted screening and treatment – interventional randomized open label clinical trial. Randomized by household to receive drug or SOC.
Study Size: 190 Covid-19 Cases (95 per arm) and 2850 contacts (15 per index case)
Study Population: Confirmed non-severe case of Covid-19 (index) and 15 contacts
Study Drug:

- **Index -** Darunavir 800 mg/cobicistat 150 mg tablets (oral, 1 tablet everyday for 7 days and hydroxychloroquine 800 mg (620 mg base) followed by 400 mg at 24 hours, 48 hours, 72 hours.
- **Contacts -** Hydroxychloroquine 800 mg (620 mg base) followed by 400 mg at 24 hours, 48 hours, 72 hours.

Primary Outcome: **Index** - throat swabs at 3 days and symptom diaries for 14 days;
Contacts: Symptom diaries for 14 days.

Inclusions: Index, PCR-confirmed with mild respiratory symptoms, male or female ≥ 18 yrs, females pregnancy test negative and willing to use contraception during study, able to take oral drugs..
Exclusions: Critically ill patients, HIV, respiratory distress, requires dialysis, history of cardiac arrhythmia, pregnant females, taking other drugs likely to interfere.

PEP STUDY: UNIVERSITY OF MINNESOTA

Post-exposure Prophylaxis for SARS-Coronavirus-2: A Pragmatic Randomized Clinical Trial

Summary

PI: David R Boulware MD, MPH
Department of Medicine, University of Minnesota
Multicenter: No
Location: Online, all US

Status: ongoing as of 17 March
Start Date: March 17, 2020
End date: May 2021

Funding/ Next Steps

State/Local funding

Documents

ClinTrials: NCT0430866

Study Aim

To test if post-exposure prophylaxis with hydroxychloroquine can prevent progression development of symptomatic COVID19 disease after known exposure to the SARS-CoV2 virus.

- Number of participants at 14 days post enrollment with active COVID19 disease.

Study Synopsis

Design: Randomized 1:1 online, Quadruple masked (Participant, Care Provider, Investigator, Outcomes Assessor)
Study Size: 1500
Study Population: Health care or household contacts exposed to COVID-19 within less than 3 days
Study Drug: Hydroxychloroquine, 200mg tablet; 800 mg orally once, followed in 6 to 8 hours by 600 mg, then 600mg once a day for 6 consecutive days, or **placebo** (vitamin) 4 placebo tablets once, followed in 6 to 8 hours by 3 tablets, then 3 tablets once-a-day for 6 consecutive days.
Outcome Measures: Self-reporting; incidence of disease; severity score

Inclusion: Healthy adults > 18 yrs old with exposure within 3 days
Exclusions: Cold or flu symptoms; allergy to CQ; Potential DDi

PRE-EXPOSURE PROPHYLAXIS (PEP)

PrEP STUDY- MORU, SE ASIA

Chloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)

Summary

PI: Prof Nick Day and Prof Nick White Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand
Sponsor: University of Oxford
Multicenter: Yes
Locations: Thailand, Laos, Myanmar, Cambodia, Viet Nam, India
Date: March 11, 2020 v1
Start Date: TBD
End date: ~12 months duration

Funding/ Next Steps

COVID-19 Therapeutics Accelerator, grant in process
Other funders?

Documents

Full protocol & synopsis here

Study Aims

- To determine if chloroquine prophylaxis prevents symptomatic COVID-19 infection in health care workers or other groups at high risk.
- To determine if chloroquine prophylaxis attenuates COVID-19 infections.

Study Synopsis

Design: The study is a double-blind, randomised, placebo-controlled trial that will be conducted in healthcare settings. They will be randomised to receive either chloroquine or taste masked placebo (1:1 randomisation).
Study Size: 10,000 total participants (200 subjects in 50 sites each)
Study Population: Healthcare workers, those working frontline (patient contact) in healthcare facilities, and other high-risk groups. Adults (exact age is dependent on countries)
Study Drug: A loading dose of 10 mg base/kg (620mg (4x155mg) for a 60kg subject) DOT, followed by 155mg daily (250mg chloroquine phosphate salt) will be taken for 3 months or until they are diagnosed with COVID-19.
Outcome Measure: PCR-confirmed COVID-19 illness and severity score. Twice daily electronic reporting of temperature and symptoms, and once monthly health care visit.

Inclusions: Adult healthcare worker, ≥ 16 yrs old; have internet enabled smartphone.
Exclusions: Hypersensitivity or contraindication to CQ, OH-CQ; taking drug with known DDi; retinal disease; QTc elongation (no EEG)

PrEP STUDY: AUSTRALIAN DEFENSE FORCE

Multi-Site, Randomized, Open-Label, Parallel-Group, Active-Controlled Study to Assess the Chemoprophylactic Safety and Efficacy of Chloroquine Against SARS-COV-2 in ADF Personnel at High-Risk of Exposure

Summary

PI: Major Scott Hahn PhD, MBBS
ADFMIDI
Gallipoli Barracks
Enoggera, QLD 4051, Australia
Multicenter: Yes
Locations: ADF Health Units, Australia
Date: March 9, 2020 v1
Start Date: TBD
End date: TBD

Funding/ Next Steps

Australian govt

Documents

Full protocol here
ADFMIDI-2020-01

Study Aim

To determine whether chloroquine chemoprophylaxis is effective in reducing the incidence of days off work due to Acute Respiratory Illness (ARI) in adults at high risk of SARS-COV-2 exposure.

Study Synopsis

Design: Randomized, open label, parallel-group active controlled
Study Size: 680 adults
Study Population: Healthy, adult volunteers who are members of the ADF and are at high risk of SARS-COV-2 infection. The study will be run over a single phase in two parts.
Study Drug: The dose to be administered orally is 500 mg chloroquine (2 x 250 mg tablets) per day for three total consecutive days (loading doses), followed by another 500 mg dose once per week for the following 10 weeks (beginning post-loading dose Day 5). The placebo (Vit C) group will receive 1 g (2 x 500 mg tablets) per day for three consecutive days, followed by another 1 g dose once per week for the following 10 weeks (beginning post-loading dose Day 5).
Primary endpoints: PCR-confirmed COVID-19 illness. Temperature recorded twice per day and any symptoms or days off from work on smartphone app, weekly visits.

Inclusion: At risk for exposure to Covid-19
Exclusions: Allery or potential DDi with either drug.

From:	Walker, Robert (OS/ASPR/BARDA) /O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=7A02E128C60F4A7195532A1545AF9556-WALKER, ROB <Robert.Walker@hhs.gov>
To:	Blatner, Gretta (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=623cb123c2324236b1db6fb9153e0bbf-Blatner, Gr <Gretta.Blatner@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=ce6824b6a92a4a4e893ea7b54e17eb3c-Lambert, Li <Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0851e89240324306b78740a4a60745e2-Johnson, Ro <Robert.Johnson@hhs.gov>; Faison, Tremel (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=2bbab0bceb1342fbbedbbcc94deeb80f-Faison, Tre <Tremel.Faison@hhs.gov>; Oshansky, Christine (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=d7bd764440b44b06af644cdcd22e42d6-Oshansky, C <Christine.Oshansky@hhs.gov>; Houchens, Christopher (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=7ac94a574bd04528b7c91bbd61893975-Houchens, C <Christopher.Houchens@hhs.gov>
CC:	Disbrow, Gary (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=0fd5845defda4dc0bb45f8fac629cf09-Disbrow, Ga <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) /o=ExchangeLabs/ou=Exchange Administrative Group (FYDIBOHF23SPDLT)/cn=Recipients/cn=53034752f35a4317aa74f46348442d39-Bright, Ric <Rick.Bright@hhs.gov>
Subject:	RE: FOR REVIEW: Policy Options for Release of SNS-Held Chloroquine and Hydroxychloroquine
Date:	2020/04/08 16:12:17
Priority:	Normal
Type:	Note

One comment from me, Gretta
Bob

From: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>
Sent: Wednesday, April 8, 2020 12:06 PM
To: Walker, Robert (OS/ASPR/BARDA) <Robert.Walker@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Johnson, Robert (OS/ASPR/BARDA) <Robert.Johnson@hhs.gov>; Faison, Tremel (OS/ASPR/BARDA) <Tremel.Faison@hhs.gov>; Oshansky, Christine (OS/ASPR/BARDA) <Christine.Oshansky@hhs.gov>; Houchens, Christopher (OS/ASPR/BARDA) <Christopher.Houchens@hhs.gov>
Cc: Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Subject: FW: FOR REVIEW: Policy Options for Release of SNS-Held Chloroquine and Hydroxychloroquine

Hi All,

Ensuring you all have seen this policy document for review from the DLG team. Comments are due back to them by 5PM today. Happy to collate comments if you send to me before 4.

Thanks
g

From: Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>
Sent: Wednesday, April 8, 2020 11:38 AM
To: Blatner, Gretta (OS/ASPR/BARDA) <Gretta.Blatner@hhs.gov>
Subject: Fwd: FOR REVIEW: Policy Options for Release of SNS-Held Chloroquine and Hydroxychloroquine

Are you collating this info from across BARDA or who is? Has it been shared with clinical and regulatory teams for review?

Sent from my iPhone

Begin forwarded message:

From: "DLGDESK (HHS/ASPR/OPP)" <DLGDESK@hhs.gov>
Date: April 8, 2020 at 11:07:25 AM EDT
To: "DLGDESK (HHS/ASPR/OPP)" <DLGDESK@hhs.gov>, "Stannard, Paula (HHS/IOS)" <Paula.Stannard@hhs.gov>, "Kadlec, Robert (OS/ASPR/IO)" <Robert.Kadlec@hhs.gov>, "Grigsby, Garrett (HHS/OS/OGA)" <Garrett.Grigsby@hhs.gov>, "Kerr, Lawrence (HHS/OS/OGA)" <Lawrence.Kerr@hhs.gov>, "Chang, William (HHS/OGC)" <William.Chang@hhs.gov>, "Sherman, Susan (HHS/OGC)" <Susan.Sherman@HHS.GOV>, "Ray Gorrie, Jennifer (HHS/OGC)" <Jennifer.Ray-Gorrie@hhs.gov>, "Strom, John (HHS/OGC)" <John.Strom@hhs.gov>, "Patel, Anita (CDC/DDID/NCIRD/OD)" <bop1@cdc.gov>, "Ethier, Kathleen (CDC/DDID/NCHHSTP/DASH)" <kbe0@cdc.gov>, "sh1@fda.hhs.gov" <sh1@fda.hhs.gov>, "Hinton, Denise (FDA/OC)" <Denise.Hinton@fda.hhs.gov>, "Mair, Michael (FDA/OC)" <Michael.Mair@fda.hhs.gov>, "Courtney, Brooke (FDA/OC)" <Brooke.Courtney@fda.hhs.gov>, "Collins, Francis (NIH/OD) [E]" <collinsf@od.nih.gov>, "Fauci, Anthony (NIH/NIAID) [E]" <afauci@niaid.nih.gov>, "Marston, Hilary (NIH/NIAID) [E]" <hilary.marston@nih.gov>, "Shuy, Bryan (OS/ASPR/IO)" <Bryan.Shuy@hhs.gov>, "Yeskey, Kevin (OS/ASPR/IO)" <Kevin.Yeskey@hhs.gov>, "Bright, Rick (OS/ASPR/BARDA)" <Rick.Bright@hhs.gov>, "Disbrow, Gary (OS/ASPR/BARDA)" <Gary.Disbrow@hhs.gov>, "Lambert, Linda (OS/ASPR/BARDA)" <Linda.Lambert@hhs.gov>, "Adams, Steven A. (ASPR/SNS)" <saa1@cdc.gov>, "Gorman, Susan (ASPR/SNS)" <spg4@cdc.gov>
Cc: "Phillips, Sally (OS/ASPR/SPPR)" <Sally.Phillips@hhs.gov>, "DeBord, Kristin (OS/ASPR/SPPR)" <Kristin.DeBord@hhs.gov>, "Dodgen, Daniel (OS/ASPR/SPPR)" <Daniel.Dodgen@HHS.GOV>, "Austin, Meredith (OS/ASPR/IO)" <Meredith.Austin@hhs.gov>, "Sheehy, Janice (FDA/ORA)" <Janice.Sheehy@fda.hhs.gov>, "Shirley, Mayo (FDA/OC)" <Mayo.Shirley@fda.hhs.gov>
Subject: RE: FOR REVIEW: Policy Options for Release of SNS-Held Chloroquine and Hydroxychloroquine

Good morning Disaster Leadership Group Members,

This is a friendly reminder to please provide your edits/comments to the "Release of SNS-Held Chloroquine and Hydroxychloroquine" policy options paper to DLGDESK@hhs.gov by **5:00 PM today**. I've reattached the policy options paper along with the International MCM Sharing Policy Framework for your convenience. Thank you to those who have already responded.

Respectfully,

Dan

Daniel Dodgen, Ph.D.
Senior Advisor
Office of the Assistant Secretary for Preparedness and Response (ASPR)
Office of Strategy, Policy, Planning and Requirements (SPPR)

HEALTH AND HUMAN SERVICES (DHHS) | O'Neill House Office Building | 200 C Street SW | Washington, DC 20515
o. (202) 245-0719
Daniel.Dodgen@HHS.Gov | www.phe.gov

From: DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Sent: Tuesday, April 7, 2020 11:48 AM
To: Stannard, Paula (HHS/IOS) <Paula.Stannard@hhs.gov>; Kadlec, Robert (OS/ASPR/IO) <Robert.Kadlec@hhs.gov>; Grigsby, Garrett (HHS/OS/OGA) <Garrett.Grigsby@hhs.gov>; Kerr, Lawrence (HHS/OS/OGA) <Lawrence.Kerr@hhs.gov>; Chang, William (HHS/OGC) <William.Chang@hhs.gov>; Sherman, Susan (HHS/OGC) <Susan.Sherman@HHS.GOV>; Ray Gorrie, Jennifer (HHS/OGC) <Jennifer.Ray-Gorrie@hhs.gov>; Strom, John (HHS/OGC) <John.Strom@hhs.gov>; Patel, Anita (CDC/DDID/NCIRD/OD) <bop1@cdc.gov>; Ethier, Kathleen (CDC/DDID/NCHHSTP/DASH) <kbe0@cdc.gov>; sh1@fda.hhs.gov; Hinton, Denise (FDA/OC) <Denise.Hinton@fda.hhs.gov>; Mair, Michael (FDA/OC) <Michael.Mair@fda.hhs.gov>; Courtney, Brooke (FDA/OC) <Brooke.Courtney@fda.hhs.gov>; Collins, Francis (NIH/OD) [E] <collinsf@od.nih.gov>; Fauci, Anthony (NIH/NIAID) [E] <afauci@niaid.nih.gov>; Marston, Hilary (NIH/NIAID) [E] <hilary.marston@nih.gov>; Shuy, Bryan (OS/ASPR/IO) <Bryan.Shuy@hhs.gov>; Yeskey, Kevin (OS/ASPR/IO) <Kevin.Yeskey@hhs.gov>; Bright, Rick (OS/ASPR/BARDA) <Rick.Bright@hhs.gov>; Disbrow, Gary (OS/ASPR/BARDA) <Gary.Disbrow@hhs.gov>; Lambert, Linda (OS/ASPR/BARDA) <Linda.Lambert@hhs.gov>; Adams, Steven A. (ASPR/SNS) <saa1@cdc.gov>; Gorman, Susan (ASPR/SNS) <spg4@cdc.gov>
Cc: Phillips, Sally (OS/ASPR/SPPR) <Sally.Phillips@hhs.gov>; DeBord, Kristin (OS/ASPR/SPPR) <Kristin.DeBord@hhs.gov>; Dodgen, Daniel (OS/ASPR/SPPR) <Daniel.Dodgen@HHS.GOV>; Meredith.L.Austin@usbordencg.mil; Sheehy, Janice (FDA/ORA) <Janice.Sheehy@fda.hhs.gov>; Blatner@hhs.gov; Shirley, Mayo (FDA/OC) <Mayo.Shirley@fda.hhs.gov>; DLGDESK (HHS/ASPR/OPP) <DLGDESK@hhs.gov>
Subject: FOR REVIEW: Policy Options for Release of SNS-Held Chloroquine and Hydroxychloroquine

Dear Disaster Leadership Group Members and Colleagues:

Thank you for your participation in COVID-19 Disaster Leadership Group (DLG) Meetings. We are soliciting feedback to inform a policy recommendation regarding whether or not ASPR should support the release of chloroquine and hydroxychloroquine for clinical trials outside the United States. These two drugs are covered by the Emergency Use Authorizations requested by BARDA and approved by the FDA.

1. **FOR REVIEW**: Please find the attached "**Release of SNS-Held Chloroquine and Hydroxychloroquine**" policy options paper for your review.

   Suspense Date: Please offer any edits to the "Release of SNS-Held Chloroquine and Hydroxychloroquine" policy options paper to DLGDESK@HHS.gov **by 5:00 PM on Wednesday April 8, 2020**.

   <<File: Release of SNS-Held Chloroquine and Hydroxychloroquine.docx >>

2. **FOR INFORMATION**: Please find the attached "**International MCM Sharing Policy Framework**" document, which is an existing policy framework for any requests to use HHS-held MCMs internationally.

   <<File: International MCM Sharing Policy Framework FINAL January 2014.pdf >>

We ask that DLG meeting participants ensure leadership within their respective HHS Staff and Operating Divisions are briefed on these materials, and that you do not forward this material beyond the distribution of this message. Please address any questions related to this request to the DLGDESK Resource Mailbox at DLGDESK@hhs.gov.

Respectfully,

Dan

Daniel Dodgen, Ph.D.
Senior Advisor
Office of the Assistant Secretary for Preparedness and Response (ASPR)
Office of Strategy, Policy, Planning and Requirements (SPPR)

HEALTH AND HUMAN SERVICES (DHHS) | O'Neill House Office Building | 200 C Street SW | Washington, DC 20515
o. (202) 245-0719
Daniel.Dodgen@HHS.Gov | www.phe.gov

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