JUUL Internal Email Thread
“Re: Turbo lite”
Dated August 10–13, 2018

From: Ian Fearon on behalf of Ian Fearon [redacted]@juul.com>
To: Marcie Hamilton
CC: Kirk Phelps; Manoj Misra; Dimitrios Zisoulis; Bryan White; Joanna Engelke; Josh Vose; Ellen Murphy; Peter Beckett
Sent: 8/13/2018 9:34:36 AM
Subject: Re: Turbo lite

Hi Marcie

I think there are 2 aspects to this - the first is safety, and ensuring that we aren't delivering so much nicotine per puff that it could be harmful. It's unlikely but a good exercise in due diligence and for sure can be done using machine yields and some modelling.

The second is efficacy; I understand that turbo will deliver more TPM than J1, but that won't necessarily translate into greater nicotine delivery into the blood. It may well do, but because so many other factors affect nicotine delivery (particle size, pH, water content, ability of nicotine to evaporate from the particles in the right place, etc) we can only know for sure with a nicotine PK study. My concern is that we will develop something that we believe will deliver more nicotine and counteract the regulatory ceiling that pushes us down from 5 to 1.7, but which may not. The consequence is that we won't satisfy a smokers nicotine need with turbo either and knowledge of the likelihood of that will help us manage this. I have been in this situation before; a multi-million pound project on an innovation that many people believed would deliver nicotine very well was canned since in the hands of users it actually delivered less than existing technologies. No lab/modelling approaches currently exist that can be used instead.

I'm on the train home but can take a call any time from 11-2 SF time today, or arrange one for tomorrow, to discuss my thoughts on timing.

Regards

Ian

Ian M. Fearon PhD
Senior Director, Clinical and Regulatory Affairs EMEA
e: [redacted]@juul.com
m: [redacted]

JUUL Labs | [redacted]

On 13 Aug 2018, at 17:16, Marcie Hamilton [redacted]@juul.com> wrote:

Hi Ian,

We aim to always make safety and health our highest priority.

I thought we said for PK we would do a paper exercise (10x safety factor) and that we would bolster this with 2 week lab tests. Based on results, we may need ph1 safety (dose escalation) study.

I'll call you to discuss the 2-week lab tests per your "PK can be done quickly and easily and in compliance with recognised standards, and if we started the study prep now we could get the nicotine data just a week or two after

having products (or prototypes) to test." comment.

Best,
Marcie

On Fri, Aug 10, 2018 at 3:40 PM, Ian Fearon [redacted]@juul.com> wrote:
Hi Marcie and Kirk
I just wanted to reiterate a view from earlier this week; I know timelines are tight but I feel strongly that we need to understand the nicotine PK of turbo lite pre-launch. It can't be determined from simple TPM mass delivery as a host of other factors impact nicotine delivery and absorption. PK can be done quickly and easily and in compliance with recognised standards, and if we started the study prep now we could get the nicotine data just a week or two after having products (or prototypes) to test. If we don't do it, we will never be able to understand if we are going to meet the market need ie better nicotine delivery than J1 to make up for EU low pod nicotine.
Happy to discuss further if you wish
Regards
Ian

Ian M. Fearon PhD
Senior Director, Clinical and Regulatory Affairs EMEA
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Marcie Hamilton
Juul Labs [redacted]

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JUUL Internal Email Thread
“Re: Turbo lite”
Dated August 10–15, 2018

From:	Marcie Hamilton on behalf of Marcie Hamilton [redacted]@juul.com>
To:	Manoj Misra
CC:	Bryan White; Dimitrios Zisoulis; Ellen Murphy; Ian Fearon; Jake Barz; Joanna Engelke; Josh Vose; Kirk Phelps; Peter Beckett; Concetta Carbonaro; David Cook
Sent:	8/15/2018 9:06:47 AM
Subject:	Re: Turbo lite
Attachments:	Turbo Lite PK study.docx

Hi,

Ian, Manoj, and I talked this morning about PK turbo-lite studies.

It is correct that the PK study is for efficacy, not safety. Therefore, the results are not gating human puffing (user studies or on the market after approval). Arguments for the PK study are to make sure we are delivering more nic/puff which validates the whole premise of turbo-lite. From a business perspective, it makes sense to do the PK study as a go/no-go gate for turbo efficacy. PK also helps us validate the paper/modeling exercise. The earliest the PK study could start is early Sept. PK is not a TPD market submission requirement. However, when we do studies, we need to provide the results in a report in the notification filing.

HPHC aerosol results (will start on at least 4 flavors w/ CYX wick and non-vented design by 8/31), and the paper/modeling exercise base on aerosol results are the gate for human puff testing.

See below for Ian's drafted initial thoughts on the proposed turbo lite PK study. This is more to provide discussion points than to have anything set in stone.

Actions:

- **Ian** will follow up the Concetta and Josh regarding PK study execution (1.7% silica vs 1.7% cotton in the same flavor)
  - **Ian** will take the lead on the protocol and informed consent form
  - **Ian** will write the PK report
  - **Ian/Josh** will keep Marcie informed regarding the PK study, especially if there are any deviations to the understandings outlined in this email.
- **David** will manage the aerosol studies
- **Jake/Marcie** will get devices to David for aerosol testing. We will have this settled by EOB Friday.
- **Jake/Marcie** will get 10 devices, 30 1.7% silica pods, and 30 1.7% cotton wick pods for shipping in early Sept (suggest mint - definitely the same flavor for study control among subjects; other options are tobacco and mango)

Best,
Marcie

On Mon, Aug 13, 2018 at 10:18 PM, Marcie Hamilton [redacted]@juul.com> wrote:
+ Concetta in that case.

On Mon, Aug 13, 2018 at 10:05 PM, Manoj Misra [redacted]@juul.com> wrote:
Hi Marcie
Our Juul clinical testing services lead by Concetta will develop protocol and study conduct with Ian guidance. They have clinical side covered. I am involvement is on science side advise.
Thanks
Manoj

On Mon, Aug 13, 2018 at 9:59 PM Marcie Hamilton [redacted]@juul.com> wrote:

I set the meeting for 8-9a PT (4-5p in England) for Wed. LMK if you want to join, and I'll add you to the meeting maker.

On Mon, Aug 13, 2018 at 9:51 PM, Marcie Hamilton [redacted]@juul.com> wrote:
Hi Bryan,

Yes. I will lead. Let me get a call with me, Ian, and Manoj to discuss next steps.

Best,
Marcie

On Mon, Aug 13, 2018 at 11:57 AM, Bryan White [redacted]@juul.com> wrote:
Thanks for the feedback and continued discussions...

As of late last week, we now have Turbo Lite pods (built at Defond with o-net w/c) in house, packaged into full RK in all 6 flavors. Given all of the uncertainty and process development work, I would propose that we push hard to test with this product as a way to force alignment and expose any issues with the nascent process. We can debate for weeks, but we now have product (and Kevin's full support) to test and find issues earlier.

Marcie / Jake - can you help coordinate with this team to get testing reserved and start deploying the product?

Thanks

On Mon, Aug 13, 2018 at 9:58 AM Manoj Misra [redacted]@juul.com> wrote:
Hi Team
Just want to make sure we all understand the difference and criteria utilized for different studies and potential use of that information for different applications. Below, I try to differentiate the differences in a non-technical way the between two analysis and also Ian pointed it very well.

- **What we generate in JUUL flavor Aerosol--SAFETY:** HPHC (Aerosol) Measurement by Smoking Machine- Provides Nicotine, TMP and other FDA recommended HPHC --> This test tell us if we have any significant, if any, HPHC compounds in flavor aerosol--> In same analysis, we calculate (paper exercise) the potential human exposure of tested HPHC at three full JUUL pod consumption/day basis, thus the SAFETY.
- **What human blood Level of Nicotine after JUUL flavor Aerosol intake-Efficacy:** PK Measure the Nicotine level in human blood: This measurement and level is depend various factors (topography, particle size, etc.) as Ian pointed out and plays a role in both product satisfaction, product efficiency and regulatory acceptance.
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- **Bottomline:**
- **Option 1:** Some folks do Nicotine PK modeling for different nicotine levels with available software means that once you have the PK from 5% of one flavor it is possible to predict the PK for lower nicotine levels (3 or 1.5%) but the aerosol generation device has to be same. In our case here if we are changing pod/device the nature of aerosol is going to be different (particle size etc.), therefore not advisable.
- **Option 2:** Conduct independent PK trial - Preferred.

Hope this help in advancing our discussion for testing plan...

Cheers

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Juul Labs [redacted]
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Bryan White

SVP, Hardware and Firmware Engineering
Juul Labs [redacted]

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Marcie Hamilton
Juul Labs [redacted]

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