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ConcePTION

WP8 – Scientific coordination, project management & sustainability

D8.9 Reports from Advisory Board and Ethics Report year 2

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Table of Contents

Abstract

This deliverable contains the assessment, guidance, and recommendations from the members of the Advisory Board of ConcePTION on project activities and compliance of these activities with IMI regulations, ethics, and scientific standard procedures. It focuses on the progress of the project during the second year.

The feedback provided by each of the members of the Advisory board is based on the presentations and discussions which took place during the virtual General Assembly meeting of ConcePTION in April 2021. The report also contains feedback and actions points provided from the Managing Team of ConcePTION.

The members of the Advisory Board agree that ethical standards for data collection, privacy protection and human participation are met in the ConcePTION project.

Advisory Board report

The aim of this deliverable D8.9 is to report to IMI on the assessment and recommendations provided by the Advisory Board (AB) on the second year of the project. The feedback provided by each member of the Advisory board is based on the presentations and discussions which took place during the virtual General Assembly (GA) meeting of ConcePTION in April 13 and 14, 2021. The virtual GA meeting provided the work packages with the ability to share a flash forward of year two of the project. The high-level communication and sustainability plans of ConcePTION were also presented.

The members of the AB were invited to attend the meeting mainly on the first day and some of the members participated during both days. PMO contacted each member two weeks before the GA and provided questions to be answered after the GA. These questions form the structure of this deliverable and contains the recommendations and feedback provided by the AB members.

The questions provided to the AB are the following:

1. *What were the strengths/areas for further improvement that you have seen in the work by the WPs as it has been presented at the GAM?*
2. *What would be recommendations for the consortium going forward on the scientific content of the work?*
3. *What would you recommend to the consortium to further strengthen the international embedding (e.g. linking to global initiatives and activities in other key regions)*
4. *What would be key considerations for the consortium as they further work on the sustainability activities?*

The members of the AB provided a report containing recommendations, guidance, and questions to the ConcePTION consortium. The report provided by the members has been collected in one single report to be submitted to IMI as deliverable D8.9.

Recommendations from the Advisory Board members

1. ***What were the strengths/areas for further improvement that you have seen in the work by the WPs as it has been presented at the GAM?***

Elizabeth Conover *MS, APRN, CGC (University of Nebraska Medical Center)*:

- It bears repeating: ConcePTION is just so impressive! ..."no other projects on this scale in the world" …public/private partnership with industry, regulators, academia and medicine.
- The demonstration studies from WP1 and WP2 are exciting. I look forward to hearing more about a minimum data set and may have some thoughts on that.
- As for WP3 and WP4, traditionally there has been a large focus on exposures to pregnant women, but not much interest in breastfeeding exposures. I am envious of the breastmilk biobank and interested in the project that uses minipigs as an example of an in-vivo way of studying breastmilk exposures. Nearly half of the questions I answer through my teratogen information service involve safety of prescribing a medication to a breastfeeding woman.
- Regarding WP5, there is often a focus on communicating results through publishing in scientific journals. As you move forward, it would be important to consider extending this to training and continuing education of healthcare providers who often struggle to handle the risk: benefit aspect of prescribing to pregnant and breastfeeding women. They also have a great deal of anxiety about where and how to obtain current and reliable information on preferred agents. The knowledge bank is an excellent beginning, but there needs to be increased emphasis on health literacy. You can have the very best data but if it cannot be effectively conveyed to providers and their patients in a way that they can utilize it you may have wasted your time. The focus groups on end-user expectations are interesting; you will want to utilize this methodology in determining whether the knowledge bank is effectively designed and implemented.

Christina Chambers, *PhD, MPH (University of California San Diego, and Rady Children's Hospital:*

Overall, each WP group has made great progress despite the challenging conditions in the last year. The following are strengths noted in the accomplishments presented:

- WP1 – development of core evidence elements and umbrella protocol; target drugs seem to represent a good range of example types of exposures
- WP2 – moving towards development of an app to report exposures using common data model

- WP3 – important progress in developing predictive models for drug concentrations in milk; piloting in minipig model.
- WP4 – finalization of SOPs for demonstration studies for 5 drugs in milk; progress on setting up protocol to collect and accept samples; validation of collection and storage procedures
- WP5 – landscape analysis final report; work towards developing prototype for knowledge bank; survey of 3000 in 70 countries re end user expectations
- WP6- progress on project glossary/interact guidelines; establishing Innovation Task Force to engage regulatory endorsement
- WP7 – work towards first use of data pipeline for characterization of data
- WP8 – receipt of feasibility assessment request with a view towards sustainability model

Jan Piasecki, *Phd (Jagiellonian University):*

- In my opinion, in terms of ethical standards for data collection, privacy protection and human participation are met. Moreover, in my opinion, the project has a very conservative approach and all-important risk to participants are mitigated (personal identified data do not leave the place of collection, informed consent is secured, and research seems to pose not more than minimal risks).

2. What would be recommendations for the consortium going forward on the scientific content of the work?

Elizabeth Conover *MS, APRN, CGC (University of Nebraska Medical Center)*:

- You state that ConcePTION will provide a 'safe harbor for all relevant stakeholders to address highly sensitive gap in the ecosystem'. However, there do not appear to be plans for prospective studies where pregnant and breastfeeding women are included in phase 3 trials. We struggle with this in the US, at least in part due to legal liability issues, which are a real stumbling block. My understanding is that liability is less of an issue in the EU. The private sector is never going to be enthusiastic about this kind of study, but it is essential if we are going to have information on agents that have the potential to be important for use in women.
- I was really interested in the knowledge bank, and whether they would have different sections for providers and the general public. Health literacy needs to be a crucial component in deciding what to include and how to portray the information for both providers and the general public. Will there be a special section for healthcare providers who may need more extensive information relayed in a professional fashion? Is the information intended for the public at around an 8th grade level?

Christina Chambers, *PhD, MPH (University of California San Diego, and Rady Children's Hospital:*

- The scientific content as outlined is excellent – just needs to be realized. In particular the comparison of findings in WP3 and WP4 will be essential

- Integration across data sources seemed to be a bit further out in scope; some discussion about the feasibility studies using only secondary data whereas prospective data could be incorporated from day 1.

Jan Piasecki, *Phd (Jagiellonian University):*

- I am focusing solely on sub-objective of the WP7: 1. *To conduct empirical ethical research on involving pregnant women in a learning health care system*.
- In my opinion, already collected data could be used to develop questionnaires to study e.g. factors of trust/distrust towards research, and learning healthcare system among pregnant and nursing women (measure quantitatively). These questionnaires can also be administrated online.
- I am not sure how this component of the project is linked to the ConcepTION App – but maybe also data from ethical empirical studies could be informative for app developers, and UIX data of the App developers can be triangulated or coupled with ethics empirical data. I see here a huge potential, since the App is at least one potential portal and interface to the learning healthcare system.

3. **What would you recommend to the consortium to further strengthen the *international embedding* (e.g. linking to global initiatives and activities in other key regions)?**

Elizabeth Conover *MS, APRN, CGC (University of Nebraska Medical Center)*:

- The United States' Task Force Specific to Pregnant Women and Lactating Women (PRGLAC) was charged with advising the Secretary of Health and Human Services regarding gaps in knowledge and research on safe and effective therapies for pregnant and lactating women. They issued two reports with recommendations, one in 2018 and more recently in 2020. Most of the recommendations from PRGLAC are consistent with the goals of ConcePTION, and there should be many opportunities for learning from each other and collaborating. ConcePTION is several years ahead in implementation and offers incentive and instruction on ways for the US to move forward.

Christina Chambers, *PhD, MPH (University of California San Diego, and Rady Children's Hospital:*

- This would be ideal and there does not seem to be much evidence of this so far – other than representation in the consortium from non-EU members. An inventory of other initiatives and a cross-talk analysis would be useful and should be updated each year.

Jan Piasecki, *Phd (Jagiellonian University):*

- I have nothing to add in this respect.

4. What would be key considerations for the consortium as they further work on the sustainability activities?

Elizabeth Conover *MS, APRN, CGC (University of Nebraska Medical Center)*:

- We struggle with sustainability issues in the US as well. We have had some luck with grants, but in general they are very time consuming and do not often result in long-term funding for larger projects. They are appropriate for targeted, short term projects, though.
- Lobbying regulators and legislators for funding has potential effectiveness. For example, OTIS/MotherToBaby is a member of The Coalition to Advance Maternal Therapeutics (CAMT) which was formed to "advocate for policies that will promote better understanding of the safety and efficacy of prescription drugs, therapeutics, and vaccines used during pregnancy and breastfeeding". This coalition includes professional societies such as the Society for Maternal Fetal Medicine and the American Academy of Pediatrics, but also lay organizations such as the March of Dimes. They primarily function to lobby congress on legislation regarding regulations, funding, and other issues pertinent to maternal health. Several times each week they meet with individual legislators to acquaint them with issues, and they offer educational sessions for larger groups as well. This strong emphasis on educating legislators is one strategy towards ultimately ensuring funding for PRGLAC priorities. ConcePTION is also initiating this, but it is one area where the US may provide some examples that could be of use in the EU.
- I have wondered what the rewards are for the pharmaceutical industry? It would be important to continue to explore this since they have potential funding for sustainability.

Christina Chambers, *PhD, MPH (University of California San Diego, and Rady Children's Hospital:*

- It was encouraging to see this being discussed seriously in year 2 of the 5-year project. It may exist, but I haven't seen yet even a very rough draft budget of what it would take to sustain basic operations – it would help to know what the minimal infrastructure cost would be, even if no specific analyses were paid for, and then what tiers of revenue would be required to maintain and grow the operation. If a membership model, or a pay as you use model is being proposed, this will impact sustainability. Several models, e.g., "basic, better, best", might also be proposed.
- Metrics to demonstrate value do not necessarily have to be restricted to improving health of the child (e.g., avoiding risky exposures and complying with recommended non-risky exposures). The satisfaction and clarity provided to the patient and provider are also valued metrics and a goal of the Consortium. Feedback on use of the Knowledge Bank should be solicited from every user, both in terms of "was the information useful?" and if yes, "did this information inform or change a decision regarding use of a medication? and if yes "how?"

- Users of the Knowledge Bank should be connected immediately to the app in order to capitalize on this pathway to capture exposures that have already taken place; and vice-versa – users of the app should be connected to the Knowledge Bank.
- It does seem like regulators need to buy into this sooner rather than later as a source of synthesis of data – and this should be international – how will the Knowledge Bank inform labels?
- Important and not too soon to think hard about governance structure – who decides whether the synthesis of data is sufficient to draw conclusions? How are discrepant opinions resolved? How are these aligned with regulators? What legal liability does the Knowledge Bank have?

Jan Piasecki, *Phd (Jagiellonian University):*

In my opinion, one of the main challenges for the project, especially in the long run, could be:

- keeping pace with digital transformation of healthcare in Europe and in other countries:
  - monitoring new sources of information
  - monitoring evolving standards of individual data control over medical information (social data cooperatives)
  - monitoring new digital technologies in digital healthcare (that could go beyond interoperability, but also thinking about digital healthcare)
- private-public partnership: empirical research about electronic health record in many different countries (both qualitative research and qualitative research) suggest that people are skeptical in respect to private companies, including pharmaceutical companies; building and maintaining trust throughout after completion of the project is important.
- communication-dissemination-exploitation: the partners of the consortium should set a certain goal for their communication and exploitation efforts, that is related especially to the knowledge-bank: it should be the place to go, for all healthcare professionals who are involved in pregnant woman care - no matter, if any drugs are involved, but when such issue is raised, then a healthcare professional knows, where she/he can resolve the problem (that is also an element of branding now and in the future).

Matthews Mathai, *MD, PhD (WHO)*

Thank you very much for the opportunity to participate in the GAM. I learned a lot during the two days and am impressed with the work that has been done thus far. My congratulations to everyone involved in this project.

Here are my reflections after the meeting:

I have been only marginally involved in the project. Two 2 hr Zoom calls are less than ideal for people who only attend an annual meeting. I was unfamiliar with some of the acronyms used in the discussion and also with some of the administrative issues. I would therefore suggest that advisors who are not directly involved in the work packages should be sent pre-

meeting reading to familiarise themselves with the status of project implementation and then provide more considered inputs.

I found the infographic providing an overview of the project very useful. I would recommend greater use of infographics in communicating the work of the different work streams more widely.

The plans to develop a knowledge base for all countries within Europe are commendable. For greater impact, this knowledge base should be made more widely available – anyone with an internet connection anywhere in the world should be able to benefit from this work.

In this context, given the concerns about the pharma industry, it would be important to get the full support of an international agency such as the EMA or WHO to affirm the reliability of the knowledge base.

Niklas Norén, *PhD (Uppsala University)*

First, I'd like to thank the project management and work-package leaders for clear presentations and excellent progress despite the on-going pandemic. I will caveat my feedback with that I have not been able to access the slides or other written information after the General Assembly Meeting, so my comments are based on what I was able to capture on the afternoon of the GAM.

WP1
This comes across as a very ambitious work program with five diverse method development and evaluation studies. What wasn't clear to me from the presentation is how will you assess whether one of the proposed methods can support accurate conclusions, I.e. to what extent the proposed approach suffices to overcome the identified challenge. It seems that for this you would need a gold standard to compare against or at least a couple of examples / case studies where you know the expected outcome of each analysis. In view of the extent and complexity of the five studies, it will be important to keep track of their scope and progress.

WP2
Much like the first work-package, this is an ambitious work programme with a variety of interesting studies planned. I was curious to know if the algorithm for quality assessment of ICSRs is intended to be automated or (partly) based on human judgment? Also, I wondered how you intend to evaluate it? The sub-project focused on predictors of safety signals is relevant and interesting. If you will fit a predictive model you will be reliant on sufficient and relevant training data. Do you plan to use historical safety signals related to pregnancy and breast-feeding for this? And if so, will there be enough such positive controls to support the fitting of a predictive model?

WP3

Work-package 3 is farther from my own area of work, but I did not from the presentation understand the exact aim of the study - does it mean to evaluate whether the mini pig is an appropriate model for human transfer of medicines from plasma to breast milk. If so, I assume that you need to know the situation in humans for the drug(s) of interest? This was not clear from the presentation, or. I missed it. Also, if there is expected variability between individual animals in the transfer of medicines from plasma to breast milk, then the sample size (3+3) does seem to be very small.

WP4
This work-package falls too far from my own area of expertise to be able to offer any detailed comments or feedback.

Regarding sustainability, I believe that IMI requires scientific publications to be Open Access which will go a long way for work-packages 1 and 2, where the main focus is method development and evaluation. It would further strengthen sustainability if you can also share any data and/or algorithms in one of the open repositories for this.

Answers to the AB and consortium action plan

Members of the Managing Team (MT) replied to the questions provided from the Advisory board as follows:

1. What were the strengths/areas for further improvement that you have seen in the work by the WPs as it has been presented at the GAM?

Comments from AB: *The knowledge bank is an excellent beginning, but there needs to be increased emphasis on health literacy. You can have the very best data but if it cannot be effectively conveyed to providers and their patients in a way that they can utilize it you may have wasted your time. The focus groups on end-user expectations are interesting; you will want to utilize this methodology in determining whether the knowledge bank is effectively designed and implemented.*

Comments from MT:
This is such an important insight, thank you. It is vital that we try to write for patients in language that they can understand. Thus, in industry over the past few years have really tried to focus on health literacy – such that in my company, for example, we have developed a global informed consent form with reading age of grade 8 – approximately 14 years old. The content for the Knowledge Bank needs to be developed, for compliance reasons, by the Public Partners – but I will personally raise this as a truly important issue for their development.

The structure of the knowledge pages in the KB, of which we already have a draft, will be starting with a summary, meant for lay public in plain language. The part below, on the same

page, will be for HCPs, abut will be visible for patients, in case they are interested to know more. The experts that will be responsible for preparing and updating the knowledge pages will be teratology services who are very experienced in providing support to patients and therefore we hope that the language will be appropriate also for the users of low literacy

2. What would be recommendations for the consortium going forward on the scientific content of the work?

Comments from AB: *You state that ConcePTION will provide a 'safe harbor for all relevant stakeholders to address highly sensitive gap in the ecosystem'. However, there do not appear to be plans for prospective studies where pregnant and breastfeeding women are included in phase 3 trials*

Comments from MT:

Thank you very much for the comment. The randomized clinical trial is considered a golden standard in drug development and there is no doubt that this type of research is very much needed. The whole ConcePTION project is set up to develop methodologies that will help to fill in the existing knowledge gap faster and on larger number of pregnant and breastfeeding women as it is happening today. By having the methodology broadly accepted (by public scientist and experts and regulators), we hope that by using health care data as well as primary collected data through pharmacovigilance will contribute to this goal. When methodologies are in place, data on many more compounds could be generated than if we had planned a few studies a few medicines in a limited number of pregnant women. As it is very well known, studies in pregnant women are having many different ethical and logistical challenges which will need long time to be overcome and we could possibly not guarantee that we could conduct such studies and deliver results within the contract period of 5 years which we signed with the European Commission.

Comments from AB: I was really interested in the knowledge bank, and whether they would have different sections for providers and the general public. Health literacy needs to be a crucial component in deciding what to include and how to portray the information for both providers and the general public. Will there be a special section for healthcare providers who may need more extensive information relayed in a professional fashion? Is the information intended for the general public at around an 8th grade level?

Comments from MT:

Same answer as in question 1. In addition – work is ongoing as to the differential options for HCPs and general public – although it must be borne in mind that any content for HCPs will ultimately be also potentially accessible to the public.

Comments from AB: WP7 - To conduct empirical ethical research on involving pregnant women in a learning health care system.

In my opinion, already collected data could be used to develop questionnaires to study e.g. factors of trust/distrust towards research, and learning healthcare system among pregnant and nursing women (measure quantitatively). These questionnaires can also be administrated online.
I am not sure how this component of the project is linked to the ConcepTION App – but maybe also data from ethical empirical studies could be informative for app developers, and UIX data of the App developers can be triangulated or coupled with ethics empirical data.

Comments from MT:
Already collected data could be used to develop questionnaires to study e.g. factors of trust/distrust towards research, and learning healthcare system among pregnant and nursing women (measure quantitatively). These questionnaires can also be administrated online.
The initial interviews and questionnaires have already been completed in the Netherlands; but the opportunity to expand the interview set is being considered in other countries and can consider the suggestions made. Any references would be appreciated.
I am not sure how this component of the project is linked to the ConcepTION App – but maybe also data from ethical empirical studies could be informative for app developers, and UIX data of the App developers can be triangulated or coupled with ethics empirical data.
The ConcePTION App aims to enhance the collection of high quality pregnancy case reports. As such, it is based on the ICH E2B format for adverse event reporting and is being modified from an existing app developed to enhance adverse event reporting through another IMI project (WEB RADR). Given time and budget constraints within the ConcePTION project the current ConcePTION app will remain based on the identified WEB-RADR format.

3. What would you recommend to the consortium to further strengthen the *international embedding* (e.g. linking to global initiatives and activities in other key regions)?

Comments from AB: This would be ideal and there does not seem to be much evidence of this so far – other than representation in the consortium from non-EU members. An inventory of other initiatives and a cross-talk analysis would be useful and should be updated each year.

Comments from MT:
Collaboration cross-regions may be more problematic and result in delays in results dissemination – and bearing in mind significant funding for this project is provided by the EMA – the participation is per IMI rules, limited to Europe. However, significant interactions with other regions are happening in the project, input from non-EU countries are requested (e.g., the 5.1.3 surveys obtained results from significant numbers of countries, many not EU), and outputs will be available on-line for all countries worldwide.
There is an active link to PREGLAC, Mother to Baby and some other institutions

4. What would be key considerations for the consortium as they further work on the sustainability activities?

Comments from AB: I have wondered what are the rewards for the pharmaceutical industry? It would be important to continue to explore this since they have potential funding for sustainability.

Comments from MT:

It is extremely important from an ethical standpoint that industry partners, when launching a new drug or as soon as possible post-launch, provide information on drug use during pregnancy or breastfeeding. We are acutely aware there are patient groups requiring drug intervention, either on an acute basis, or chronic, that need this important information – and as a corporate responsibility to give back to Society – we are committed to do this.
Reward for industry can be on different fronts: **a.** conducting pharmacoepidemiology studies in a much broader population than individual databases and with the methodology agreed by regulators; **b.** the milk biobank of milk samples collected and stored according to standards acceptable for medication transfer studies could speed up the studies of medicine transfer into breast milk, shortening the time and resources need for lengthy human lactation studies; **c.** the network of centers that conduct lactation research is a great basis for conduction prospective clinical trials.

Comments from AB: It may exist, but I haven't seen yet even a very rough draft budget of what it would take to sustain basic operations – it would help to know what the minimal infrastructure cost would be, even if no specific analyses were paid for, and then what tiers of revenue would be required to maintain and grow the operation. If a membership model, or a pay as you use model is being proposed, this will impact sustainability. Several models, e.g., "basic, better, best", might also be proposed.

Comments from MT:

Thank you for this – we are extremely sensitized to the need for sustainability and thus have started early in this planning. However, we are still at an early stage to estimate budgets required, but planning is now in action to work with the individual work packages to gain greater granularity.

Comments from AB: It does seem like regulators need to buy into this (app – Knowledge Bank) sooner rather than later as a source of synthesis of data – and this should be international – how will the Knowledge Bank inform labels?

Comments from MT:

We anticipate the harmonization of EU labels through enhanced linkage between inputting data sources to inform label updates through this project. However, this will not eliminate the need for an informed data bank that will inform patients appropriately outside of the lengthy label update process.

The intention is that the data generated in our 4 content WPs (1. secondary use of health data, 2. Prospective data collection, 3. Preclinical lactation model and the PBPK model, 4 human lactation studies and milk biobank) will prepare the methodology to generate information of the quality that can be included in the label. We also intend to use this information to inform the advice to pregnant and breastfeeding women though the knowledge bank. This KB on its own will be will not inform the label, but rather the users, e.g. patients and HCPs.

Comments from AB: One of the main challenges for the project, especially in the long run, could be:
- keeping pace with digital transformation of healthcare in Europe and in other countries (monitoring new sources of information, evolving standards of individual data control)

Comments from MT:
Absolutely correct – and this must be part of the overall sustainability project – the ability for any future entity to be able to adapt to the digital age appropriately

Comments from AB: It would be important to get the full support of an international agency such as the EMA or WHO to affirm the reliability of the knowledge base.

Comments from MT:
Absolutely correct – and this will be a key aim of the sustainability enterprises

Comments from AB: **WP2 -**I was curious to know if the algorithm for quality assessment of ICSRs is intended to be automated or (partly) based on human judgment? Also, I wondered how you intend to evaluate it? The sub-project focused on predictors of safety signals is relevant and interesting. If you will fit a predictive model you will be reliant on sufficient and relevant training data. Do you plan to use historical safety signals related to pregnancy and breast-feeding for this? And if so, will there be enough such positive controls to support the fitting of a predictive model?

Comments from MT:
The clinical quality of ICSRs is not only determined by just the presence or absence of information in the various (ICH-E2B(R3) fields, but also by the content of information provided in dedicated (text) fields. Although a number of aspects assessed can be automated, a remaining number of aspects that will be assessed in the algorithm for quality assessment will still be based on human judgment.
Validation will be based on a selected number of 90 representative reports/cases from 6 different data sources (15 per source). The assessment of the clinical quality by experts in the field of assessment of pregnancy related cases will be the gold standard. This training dataset will be used for the weighing of the parameters. As a final step we will test the performance of the revised version of the questionnaire. A minimum of 10 experts will use

the tool to assess another 90 reports/cases in a separate test-set. (15 per data source). The performance of the quality tool will be expressed in terms of specificity and sensitivity.

In respect to the question of the study into predicators of safety signals we will have to rely on historical safety signal data only. We considered using a historical overview of safety signals assessed by EMA over the past 20 years as a gold standard. We envision a relative low number of signals, so currently plan to analyse the associations by means of a prediction model only. A validation and testing phase is not planned for the same reason.

Comments from AB: **WP3 -** does it mean to evaluate whether the mini pig is an appropriate model for human transfer of medicines from plasma to breast milk. If so, I assume that you need to know the situation in humans for the drug(s) of interest? This was not clear from the presentation, or I missed it. Also, if there is expected variability between individual animals in the transfer of medicines from plasma to breast milk, then the sample size (3+3) does seem to be very small.

Comments from MT:

By an extensive literature review on the lactation physiology of many laboratory animals and humans, it became clear that the model closest to human lactation physiology is the minipig. We are conducting preclinical studies with selected compounds and those same selected compounds are also being investigated in human lactation demonstration studies. Based on the data obtained, there will be model developed that could predict the medicine breast milk concentration within a certain concentration, better that this can be done from a rat model. This will greatly help the fist label for a newly launched medication before the lactation studies could be conducted.