

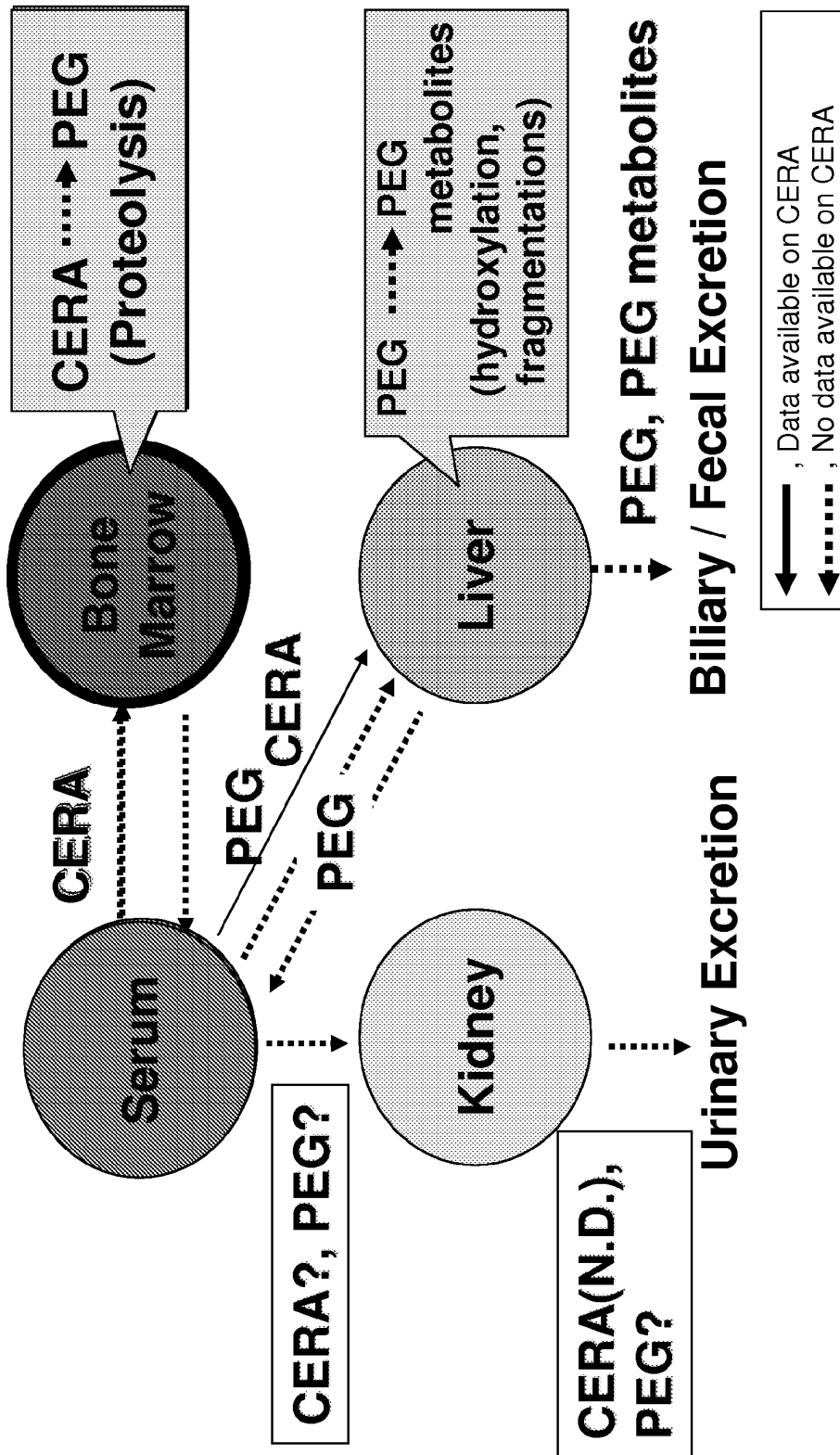
Speculative Diagrams (HVs)

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Suggested Elimination Pathways of CERA & PEG in Healthy Volunteers



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Why do we concern about the elimination of PEG in Hemodialysis Patients?

- *The major target population of CERA is CKD patients undergoing hemodialysis.*
- *In both EU and US, the average hemodialysis period is known to be 2- or 3-years, because kidney transplantations are being frequently carried out for the patients.*
- *Unfortunately, however, as far as the medical practices in Japan are concerned, the kidney transplantations are rarely done, and consequently the hemodialysis period is longer than 10-years.*

Glomerular Filtrations vs. Hemodialysis

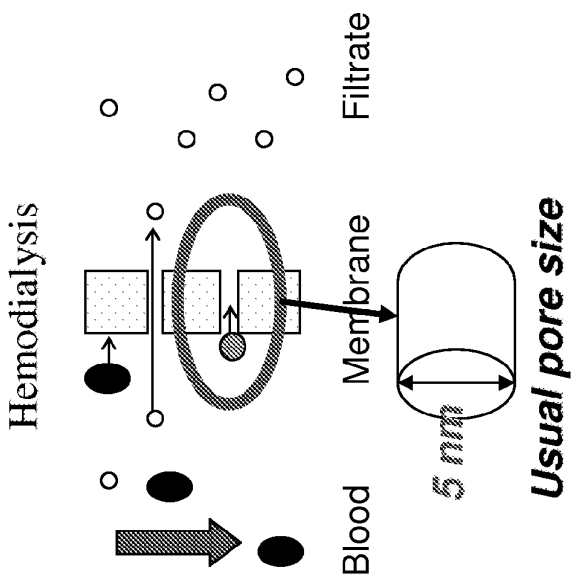
- *Glomerular Filtrations*

- 30 kDa of PEG is filtrated via glomerular apparatus within the kidney.
- 30 kDa of PEG has a diameter of about 8 nm, whereas the pore size of the glomerular basement membrane is within the range of 3-5 nm.
- Nevertheless, the PEG flexibility and deformability together with its rod-like conformation allow for the filtration of PEG.

(Adopted from Nakaoka R. et. al., *J. Control. Release* 46 (1997) 253-262)

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- *Hemodialysis*



- The usual pore size of the HD membrane is similar to that of the glomerular basement membrane.
- However, the pore size of all dialysis membranes are not always available.

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PEG Elimination in Hemodialysis Patients

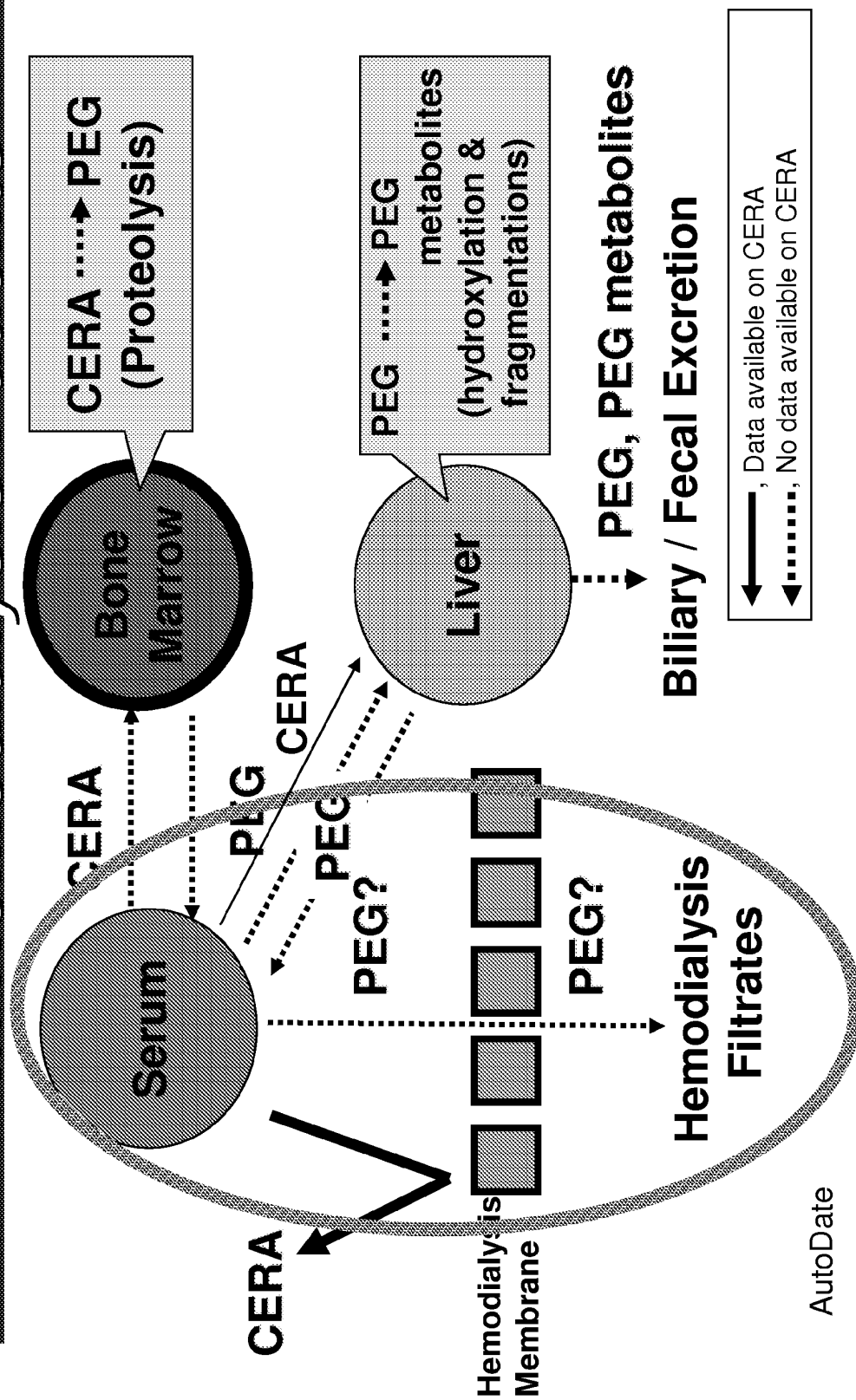
- ***The PEG moiety of 30 kDa is thought to be filtrated through the dialysis membrane possessing the usual pore size.***
- ***As to the elimination of the PEG moiety, if the dialysis membrane whose pore size is smaller than that of the glomerular basement membrane were to be employed, however the contribution of the hepatic metabolism and the fecal excretion of PEG would be much greater.***

Speculative Diagrams (HD)

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Suggested Elimination Pathways of CERA & PEG in Hemodialysis Patients



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Summary of Suggested Elimination Pathways of CERA

- *CERA is noticeably taken up by the EPO receptor localizing the bone marrow cells.*
- *The EPO moiety within the CERA structure is undergone by the proteolytic reactions in the bone marrow cells, resulting in PEG moiety formation.*
- *The residual PEG moiety within the CERA structure predominantly is excreted into the urine.*
- *The residual PEG moiety within the CERA structure is suggested to cross the dialysis membrane of the normal pore size employed for the dialysis patients.*
- *If the dialysis membrane whose pore size is smaller than that of the glomerular basement membrane were to be employed, however the contribution of the metabolism and the fecal excretion would be much greater in the elimination of the PEG moiety.*

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Points-to-Consider

- *We have suggested several elimination pathways of CERA based on the circumstantial evidences reported by EPO & PEG.*
- *While showing the suggested elimination pathways of CERA to the regulatory agency is important, the agency may require the study data in which CERA is employed.*
- *Therefore, the willingness of Chugai is that a small scale additional PK studies after administrations of CERA will have to be done.*
- *The rationale behind this idea is that the urinary excretion and the filtration of PEG are thought to be dependent upon the disease status, i.e., PreD, HD or CAPD, and upon the pore size of hemodialysis membrane.*

Proposal to Roche

- *To investigate the metabolism and excretion patterns of ¹⁴C-CERA in nephrectomized rats.*
- *“ The mass-balance studies using ¹⁴C-CERA ”to be performed in PreD patients & HV’ s.*

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“Thank you for your attention”

Kiyo

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