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# Pharmacokinetic Modeling Concepts: Compartmental and Non-compartmental approach for Drug Designing

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## Abstract

*Pharmacokinetic modeling helps to estimate the ADME parameters of all the natural and synthetic drug substances in humans and animals. There are two types of approaches for predicting the kinetic processes inside the body i.e., model approach and model independent approach. Model approach is further divided into compartmental and physiological models and model independent approach consists of non-compartmental models. Compartmental modeling is the most widely used approach. It visually shows the rate processes of drug deposition and also predict the drug concentration time graph. Compartmental model consists of catenary and mammillary models. Mammillary models can either be one compartment, multi compartment or two compartments. The physiologically based pharmacokinetic models consists of compartments that correlates with various body tissues, connected by blood circulatory system. Another name for non-compartmental analysis is model-independent approach that means it does not require any compartment model.*

**Key Words:** Pharmacokinetic, Models, Compartments, Parameters, Drug, Concentration

## Introduction

Pharmacokinetics is the analysis of the absorption, distribution, metabolism, and release of a drug in a specified amount of time. Drug levels are usually confined to blood or plasma. Pharmacokinetic data studies comprise of evaluating the concentration of plasma-time data and measuring pharmacokinetic factors describing drug status (Yamaoka, Nakagawa & Uno, 1978). Pharmacokinetic Model Approach is referred as a mathematical method for forecasting the absorption, distribution, metabolism, and Excretion (ADME) of artificial or chemical materials in humans and animal entities. Pharmacokinetic (PK) models imitate the drug concentration levels as they are the mathematical tools in the blood before their actual administration (Brown, Delp, Lindstedt, Rhomberg, & Beliles, 1997). These types have endless implications in the production of novel drugs and clinical activities.

Pharmacokinetics models are developed for specifying changes that takes place in the drug in the body and the rules which regulate these results (Schlender et al., 2016). Many functional models are developed to simplify the study of pharmacokinetics. The construction of the PK model relies on many correlated components (e.g. AUC).

The movement of drugs in the body is a complicated procedure of interpretation and inspection. Therefore, two main perspectives for the learning of the magnitude of different kinetic procedures for drug acquisition across the body are:

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- Model approach (Compartmental analysis & Physiological Modeling)
- Model independent approach (non-compartment analysis)

The Pharmacokinetics model is an intermediate piece of drug development designed for the model. It is done in ways that are not in rooms or rooms. The non- compartment model is usually measured by AUC and several different parameters, such as Cmax, Cmin, and Tmax. The time points are close, the precise model not made in the room shows the real formation of the torture time curve. The housing model is based on linear or non-linear dimensions. The model is based on a kinetic study to define and predict the torture time curve.

When formulating a pharmacokinetic inquiry, one needs to take in mind the procedure employed for data studies, because a number of options are present, each having their own pros and cons depending on the conditions (Denti, Mirochnick, & Cressey, n.d.).

Out-of-room examination is very trouble-free to utilize and sum up pharmacokinetic approaches by means of low concentration but can only be used if a pharmacokinetic profile is obtained for each study. Physiologically based pharmacokinetics is a complex speculation tool combined with silico policy particulars about the human body and the chemical and physical properties of the drug being studied (Reddy, Iii, Lave, & Andersen, 2013). This tool is plotted to work with small or no data and exhibits only in utmost circumstances.

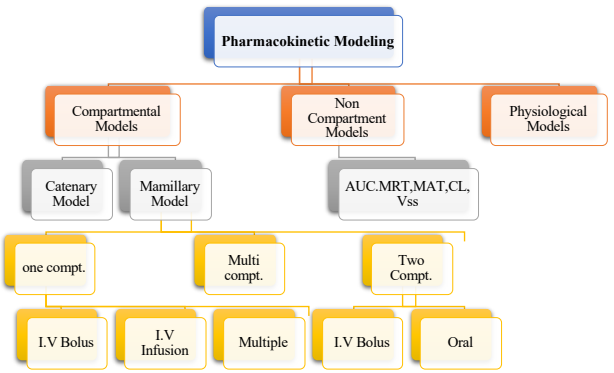


**Figure 1:** Types of pharmacokinetic modelli

## Pharmacokinetic Modeling

Pharmacokinetic model comes up with mathematical countenance to evaluate the pharmacokinetic profile of drugs across the body

### Implemented in

- Fluctuations in the drug conduct of the patient
- Anticipating conc. Medicinal characteristics of different fluids of body by dose
- Calculates the mean dose of each patient
- Evaluating the balance between different naming
- Defining drug interactions

Pharmacokinetic models are thought to be the structures used to explain the effect of a drug on the biological system that follows its administration.

### Why Model Data

Modelling approach is employed due to the following three reasons:

1. Descriptive: in order to explain the kinetics of drug in an easy manner.
2. Predictive: for forecasting the drug time after giving multiple doses on the basis of data of single dose, to tell the drug's absorption study from the intravenous data.
3. Explanatory: to describe ambiguous observations.

## Compartment Models

Due to the extensive complications of the body, drug kinetics are repeatedly clarified to be shown by one or more tanks, or compartments, which are reversibly connected to each other. A compartment is assumed to be a group of tissues which have same blood flow; however, it is not a real anatomical or physiological

region. The drug is assumed to be evenly disseminated inside each compartment.

Compartmental pharmacokinetics approach explains the elimination of a drug by splitting the body in one or more than one parts. Group of tissues having the similar blood and drug interactions are referred to as a chamber. The room is a biologic and anatomic zone. The chamber consists of different similar organs and tissues. Distinct rooms do not have first-hand accommodation and body composition. In isolated procedures, the transformation of drug concentration with time is calculated employing kinetic models.

The most extensively used procedure for mass production of pharmacokinetic drugs is compartmental analysis. (Prabu, Suriyaprakash, Ruckmani, & Thirumurugan, 2015). These models simply combine test data and allow the artistic formula to measure drug over time. Since the rooms are mythical in nature, the models of the rooms are based on speculation.

### Single-Compartment Model

This approach contemplates all the body tissues and organs to be considered as one massive bucket: the central compartment. The drug comes in the central compartment from exterior of the body and then depart from the central compartment. In this activity, drug redistribution does not take place.

When the drug is administered intravenously, the drug sets foot into the central compartment. The drug is eliminated from the central compartment as the organs taking part in drug elimination, mainly liver and kidney, are well-perfused tissues (Kok- Yong & Lawrence, 2015).

### Two-Compartment Model

In this model approach, the organs and tissues are subjected in two compartments: one central compartment and another peripheral compartment. The drug plasma concentration seems to decompose in a way explained by different exponential phases (Dvorchik & Vesell, 1976).

The overall volume of drug in the system in this model is essentially the sum of the drug available in the central compartment and the drug available in the tissue compartment.

### Three-Compartmental Model

In this model three compartments are explained: the central compartment (shows the plasma); the extremely perfused compartment (depicts the organs and tissues highly perfused by the blood); the barely perfused compartment (shows the organs and tissues barely perfused by blood)

### Suppositions of Compartmental Models

- The body is depicted as a sequence of compartments are organized in series or parallel to one another.
- The extent of drug motion among compartments is explained by first order kinetics.
- Rate constants are employed to show the rate of entrance in and out from the compartment.
- A statistical evaluation of plasma concentration time data is a procedure employed to discover number of compartments.

### Implementations of Compartmental Modeling:

- It is uncomplicated and flexible approach and extensively used.
- It provides a perceptible portrait of different rate process engaged in drug disposition.
- It is fruitful in anticipating drug concentration time profile in normal and also disease composition.
- It is advantageous in associating level of drug in plasma in therapeutic and toxic concentrations.

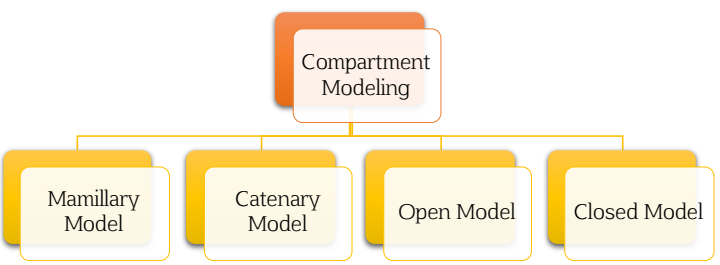


**Figure 2:** Type of compartmental modelling

## Mammillary Model

This model mainly consists of a central compartment and one or more peripheral compartments attached to it. The central compartment consists of blood plasma and extremely perfused organs for example lungs, liver, kidneys, etc. that homogenize instantly with the drug.

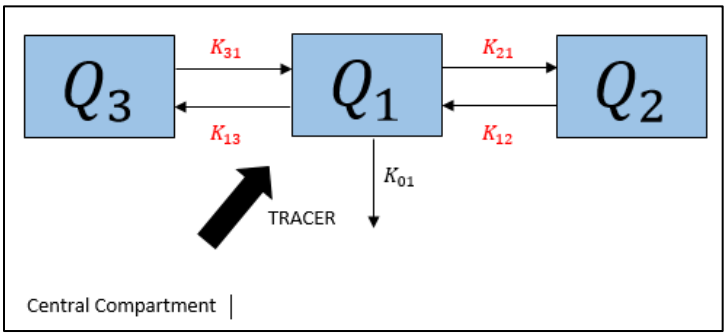


**Figure 3:** Mammillary Model: Showing the Central and Peripheral Compartment

The drug at first hand is assimilated in this compartment (i.e. blood). Elimination also takes place in this compartment because the main organs taking part in elimination are kidneys & liver, the extremely perfused organs and due to this reason they are thought to be instantly available to drug in the systemic circulation (Shuenn-Tsong Young & Kuang-Ning Hsiao).

## Catenary Model

In pharmacokinetics, the mammillary model should be differentiated from the other kind of compartmental model that is the catenary model (Holz, 2001). In this model, the compartments are linked with each other in a series like chambers of a train. Whereas, the mammillary model can be compared to that of the chambers similar to the satellites because they have a central compartment and others revolve around it. But this phenomenon is not noticeable physiologically or anatomically because different organs are connected by direct route with blood compartment. Therefore, this model is not commonly used.

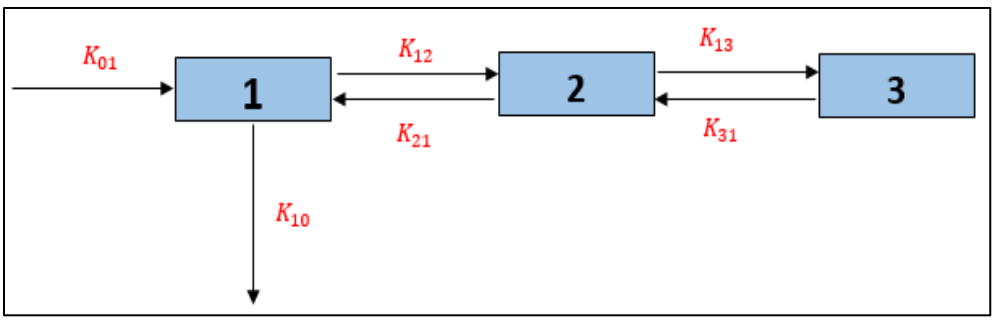


**Figure 4:** Catenary Model: Showing the Series of Compartments Joined like a trail (rarely used Model)

## Open Model

An excretory mechanism is employed for the elimination of the drug dose that is given from the body.

## Closed Model

The dose of drug is not eliminated from the body

## Chemistry Behind Single Compartment Model

The drug concentration time course finds out after administering the drug can be determined competently by presuming the body as single well merged compartment with disposition process first order (Ahmed, 2015).

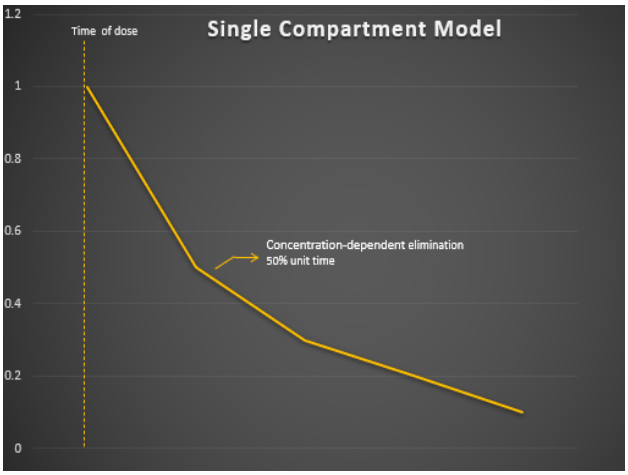


**Figure 5:** Graphical Representation of Single compartment Model

The body composed as a single kinetically equivalent component to the drug movement with no barriers and restrictions.

First order process is Elimination with a first order rate constant.

Drugs moves in and out of the compartment dynamically then Input rate will be higher than the output rate.

## One Compartment Open Model

The word open shows that the input of the drug (availability) and output of the drug (elimination) are one directional and that from the body, the drug can be excreted.

## Apparent Volume of Distribution

It is the fluid volume; the drug will apparently distribute itself into.

$$Vd = \frac{\text{Amount of drug in the body}}{\text{Plasma drug concentration}} = \frac{X}{C}$$

Several one-compartment open model can be defined on the basis of Input rate as

1. Administration of Intravenous Bolus.
2. Continuous Intravenous Infusion administration.
3. Administration by Extravascular route and follows zero-order absorption.
4. Extravascular Administration, first-order absorption.

## Multi Compartment Models

- Preferably an actual model of Pharmacokinetic should be the one that has a constant of rate for every tissue that go through equilibrium condition. (Carlander, Li, Jolliet, Emond, & Johanson, 2016).
- Consequently, the preferred technique is to combine together tissues dependent on their characteristics of distribution being identical.
- The disposition of drug takes place by first order mechanism.
- By administering drug through Intravenous Bolus and by noticing the way the concentration of plasma decreases along with time, the Multi-compartment features are best defined.
- The number of kinetically equivalent compartments into which the drug will disperse and appeared indicated by a plasma level-time profile should be explained numerically.

The two-compartment model is the easiest and the most typical that categorizes the tissues of the body into 2 categories:

1. The Central compartment or The Compartment one
2. Peripheral compartment (Tissue compartment) or the compartment two

## Non-Compartmental Analysis

The non-compartmental analysis is also referred to as model-independent approach. It does not include the hypothesis of particular compartment model. The non-compartment model assumes that an individual or organism is one homogeneous compartment only (DiStefano & Landaw, 1984). It has assumption that

blood-plasma concentration of the drug is a real representation of concentration in other tissues and drug elimination is directly proportional to drugs concentration in the individual or organism. Non-compartmental approaches are more flexible sometimes, and for bioequivalence studies, it is appropriate. However, this method is based on idea that the linear kinetics are followed by drugs and metabolites, and on this assumption, method can be extended to any one of compartment model. (Popovic et al., 2010).

For calculating PR parameters, Non-compartmental modeling methodology is used. For example, the trapezoidal rule calculates the AUC; the drug dose and the AUC is used to determined clearance (CL); Concentrations and time points are used to calculate the Cmax and Tmax; the last two to four sampling time-points are used to calculate half-life typically.(MENGE et al., 2011). The more precise non-compartmental model will be, the more nearer time points are, depicts real form of concentration-time curve.

The method of non-compartmental includes gathering experimental data based on the principle of the statistical moment after a single drug dose. If we contemplate the course of time for drug's plasma concentration as a statistical distribution curve, then:

$$MRT = \frac{AUMC}{AUC} \qquad AUMC = \int_0^\infty C\,t\,dt$$

Where,

- MRT is mean residence time,
- AUMC is area under the first-moment curve,
- AUC is area under the zero-moment curve,

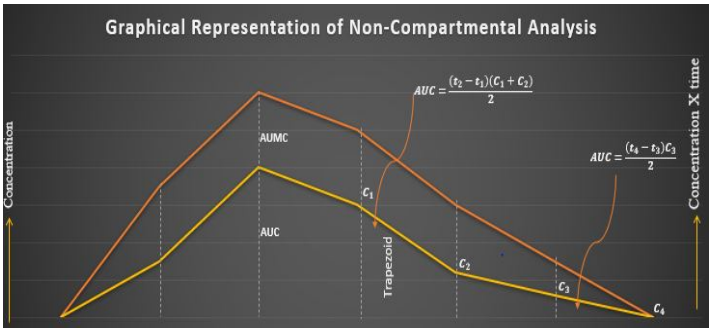


**Figure 6:** Graphical Representation of Non-Compartmental Analysis

A graph of plasma drug concentration & time (i.e.C.t) verses time from zero to infinity is used to obtain AUMC. Plasma drug concentration verses time graph from zero to infinity is used to obtain AUC.It is expressed by equation mathematically.

$$AUC = \int_0^\infty C\,dt$$

The AUMC and AUC can be determined from these graphs by the trapezoidal rule practically. Before being eliminated the mean quantity of time drug spent in the body is known as MRT.

## Applications

- It is frequently being used to determine main parameters of pharmacokinetics like apparent volume of distribution, bioavailability, and clearance.
- Technique is helpful in assessing Absorption rate of drug, half-life, and 1st order absorption rate constant.

## Physiological Based Pharmacokinetic Models

Using known physiology, PBPK models are compose of greater compartment numbers that refer to several body tissues & organs. Through rate of flow that parallel the circulation of blood, these compartments are related. The approximation of the usual Pharmacokinetic parameters, e.g., clearance (CL), volume of distribution (Vd), and effective half-life (t1/2) are provided by these models like the more empirical models. (Jones & Rowland-Yeo, 2013). They are based on known functional and structural data. So, presents more original picture of disposition of drug in different organs and tissues.

A classic PBPK model schematic representation is given in Figure 7. The volume or weight of tissue and flow rate of tissue blood that is specific and distinctive to the kind of interest is used to define each compartment. In the "System-Related Input Parameters "segment, these "system "specific characteristics, that differ over the species are explained in detail. These compartments typically

incorporate the body main tissues which includes namely, adipose, bone, brain, heart, gut, liver, kidney, muscle, lung, spleen, and skin. (Rowland, Peck, & Tucker, 2011). However, reduced models have been further explained in some cases that "lump" tissues with alike properties of flow rate of blood together to decrease the number of compartments and the altogether model complication (Nestorov, 1998). Either permeability or perfusion rate limitation is used to describe typically each tissue. (Jones, parrott, Jorga, & Lave, 2006).

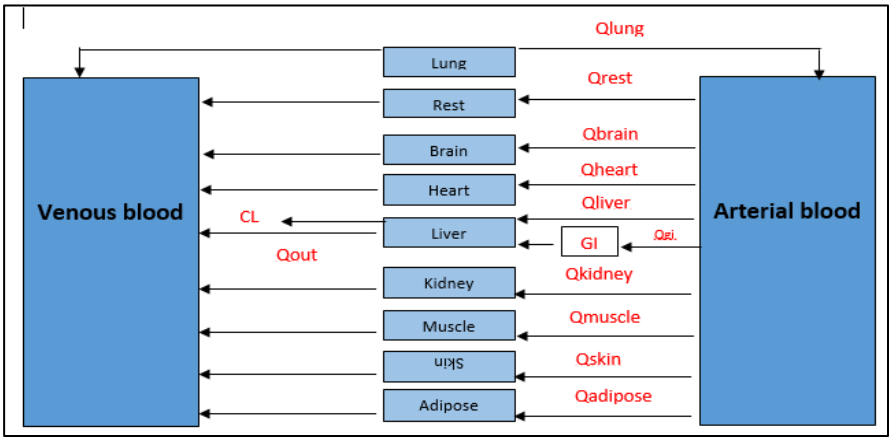


**Figure 7:** Schematic Representation of PBPK Model

Similar perfusion properties tissues are categorized into single compartment. E.g. liver, lungs, kidney, and brain are categorized as quickly homogenizing tissues. While slowly equilibrating tissues are adipose and muscles

- On known functional and structural data, models are based on.
- Drug distribution to various organs and parts of body is by Blood flow.
- Organ size (volume of tissue) and concentration of drug are obtained.
- It predicts realistic tissue drug concentration.
- Only applied to animal species and it may be extrapolated and extended to human.
- There may be a change distribution of drug from one animal species to another due to physiological factors.
- There is no requirement of data fitting.
- In the various tissues, the concentration of drug is predicted by size of organ tissue, flow of blood, and drug tissue-blood ratio which is experimentally determined.
- Distribution can be affected by the Pathophysiologic conditions.

## Pharmacokinetics of Volume of Distribution

Perfusion or permeability limit the distribution of drug into a tissue. When the membranes of tissues show no barrier to diffusion then in this case Perfusion-rate-limited kinetics will apply.

$$\frac{dQ_I}{dt} = F_i \left( C_{art} - \frac{Q_i}{P_i V_i} \right)$$

Blood flow, if drug is distributed mainly by the blood, as it is usual the case, is then the limiting factor to distribution in the different cells of the body (Alavijeh, Chishty, Qaiser, & Palmer, 2005). For small lipophilic drugs, it is mostly true. The immediate rate of entrance for the amount of drug in a compartment is similar to (blood) volumetric rate of permeate the organ times the incoming concentration of blood under perfusion limitation.

## Drugs which follow Physiological Model

- Thiopental (anesthetic): there is limited blood flow.
- Nicotine (Stimulant): In this case blood flow is limited.
- Lidocaine (Antiarrhythmic): In this case blood flow is limited.
- Methotrexate (Antineoplastic): In this case Blood flow is limited.

**Table 1.** Difference between Compartmental and Non-Compartmental Analysis

| Compartmental Analysis (CA) | Non-Compartmental Analysis (NCA) |
|---|---|
| Compartmental techniques contemplate the body to comprise of a fixed number of compartments for example blood and other organs and tissues that are linked together, well-mixed, and are kinetically homogeneous. | Non-compartmental analysis (NCA) methods are known as model independent. |
| To explain the PK of the drug, the pharmacokineticist makes some supposition and builds models based on the analysis of nonlinear regression. | They do not depend on body compartment hypotheses, and they appear to have more reliability from analyst to analyst. |
| There is the possibility for variation from one analyst to another in the performance of the study, since the parameters used to create the PK model might be quite different. | To calculate PK parameters, the NCA depends almost entirely on algebraic equations, rendering the analysis less complicated than compartmental approaches. |
| | NCAs also appear to be quicker to execute and more cost-effective. |

**Table 2.** Common Pharmacokinetic Parameters and their Units

| S. No | Pharmacokinetic Parameter | Abbreviation | Fundamental Units | Units Example |
|---|---|---|---|---|
| 1 | Area under the curve | AUC | Conc. x time | µg x hr/ml |
| 2 | Total body clearance | CLt | Volume x time | Liters/time |
| 3 | Renal clearance | CLr | Volume x time | Liters/time |
| 4 | Hepatic clearance | CLh | Volume x time | Liters/time |
| 5 | Apparent volume of dist. | Vd | Volume | Liters |
| 6 | Vol. of dist. at steady state | Vss | Volume | Liters |
| 7 | Peak plasma drug conc. | Cmax | Concentration | mg/l |
| 8 | Plasma drug concentration | Cp | Concentration | mg/l |
| 9 | Steady-state drug conc. | Css | Concentration | mg/l |
| 10 | Time for peak drug conc. | Tmax | Time | Hr |
| 11 | Dose | Do | Mass | Mg |
| 12 | Loading dose | Dl | Mass | Mg |
| 13 | Maintenance dose | Dm | Mass | mg |
| 14 | Amount of drug in the body | Db | Mass | mg |
| 15 | Rate of drug infusion | R | Mass/time | mg/hr |
| 16 | First order rate constant for drug absorption | Ka | 1/time | 1/hr |
| 17 | Zero order rate constant for drug absorption | Ko | Mass/time | mg/hr |

## Conclusion

Pharmacokinetic Modelling is mathematical tool for predicting ADME of synthetic and chemical substances in human and other species. Compartment approach represents the rate processes of drug deposition and predicts drug concentration time graph while non-compartmental approach depends on statistical moment's theory in which experimental data is collected after administrating single dose of drug. Physiological approach based on anatomical and physiological data, so it represents practical image of drug disposition in different tissues. Compartmental model consists of catenary, mammillary, open, and closed models. Mammillary Model can either be one compartment, two compartment and multi-compartment. One compartment model consists of. I.V bolus, I.V Infusion and Multiple sections while two compartment consists of I.V bolus and Oral sections. Catenary model is not observable functionally and structurally as various organs are not linked directly to blood compartment. Compartmental Modelling gives visual representation of rate processes involved in disposition of drug. For calculating PK parameters, non-compartmental approach is used. It is concluded that Pharmacokinetic models is expression for course of drug throughout body after its administration and computation of PK parameters.

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