Status quo and Future in Developments of Combination Medicinal Products

Indication: Calm, Sleeping Pills, package end of ’70
Ingredients: Extr. Valerian., Humulus lup., Viscum alb., Adonis vern., Aminophenazon, Calc.glucon.,
Sodium diethybarbituricum , Acidum phenylethybarbituricum, Potassium bromatum
Diethylbarbituric acid (with sleeping abutting effect) was synthesized in 1903.
Since 1992 they are no longer permitted in Germany and Switzerland as such.

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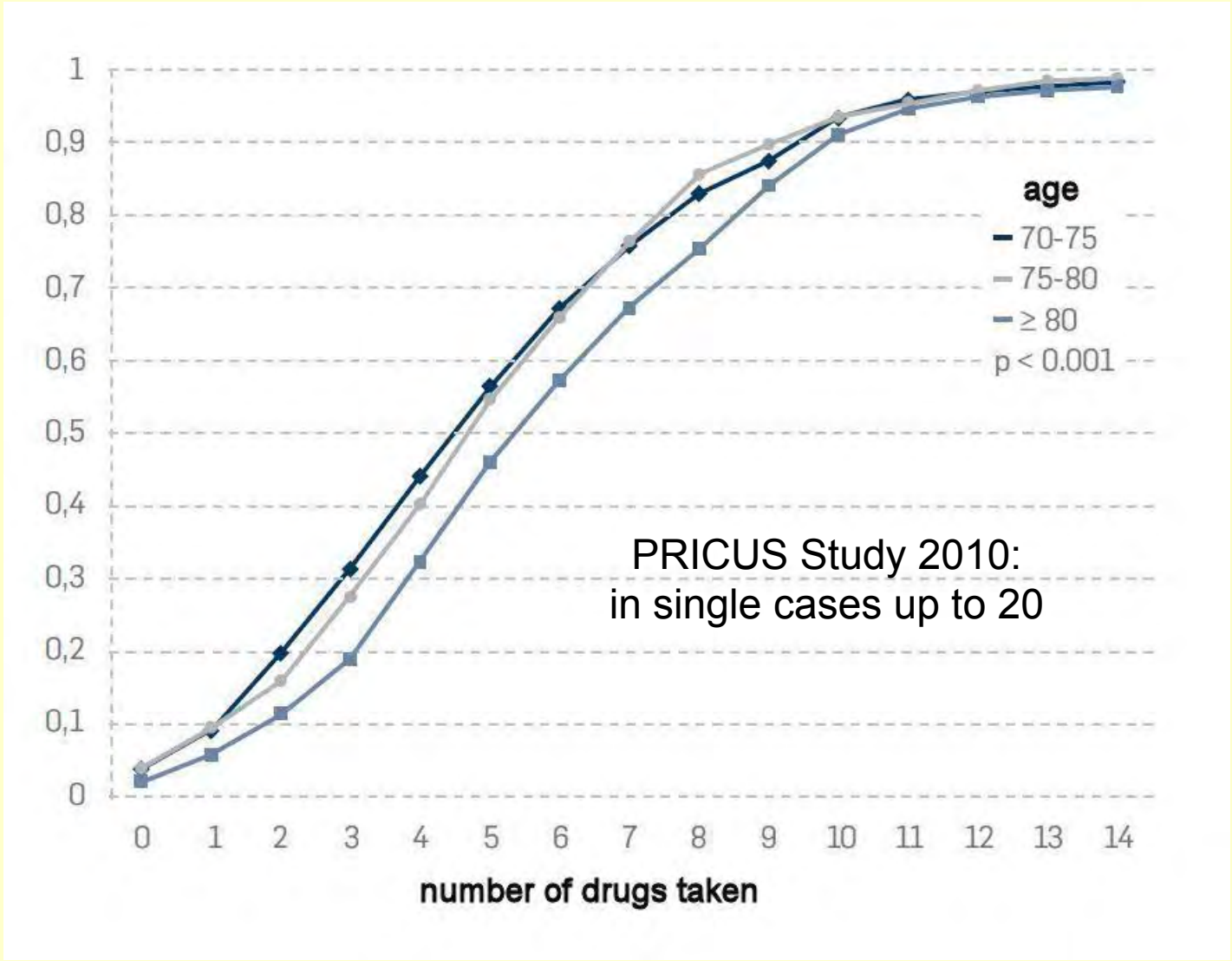
Former President of the Federal Institute for Drugs and Medical Devices (BfArM), Bonn
Former Director of the German Institute of Medical Documentation and Information (DIMDI), Cologne



The frequent argument against combinations of drugs are risks that may occur. It is to assume that the multiple interaction options are not examined (particularly for multi-medications) with up to 20 or more individual drugs.

Former General Principles:

Drugs with multiple active ingredients (combination products) offer, as compared to those with one drug (monotherapy components), rarely benefits. Drug therapy requires but usually the individual dosage of individual drugs. For the evaluation of such fixed combinations, therefore it must be determined first whether the mixture of the individual components is appropriate. If this judgment is not positive, a proof of efficacy is unnecessary, because the particular combination principle may not be recognized as a useful drug, no matter what scope.

BUT: The Crout‘s criteria do not intend to prevent any use of the fixed combination preparations.

For example, if older people in the course of a day must take more active substances, it may be helpful to administer them in combination, in order to facilitate the intake of necessary medicines.

Crout‘s Criteria

1. Each component must make a contribution to the claimed effect.

2. The dosage of each component (amount, frequency, duration) must be such that the combination is safe and

effective for a significant patient population and requiring such concurrent therapy as defined in the labeling for the drug.

3. Special cases of these general rules apply where a component is added either (1) to enhance the safety or effectiveness of the principal active ingredient,

or (2) to minimize the potential for abuse of the principal active ingredient.

Clearly, an essential feature of any rational combination product is that each ingredient contributes to the overall effect.

CROUT, J. R „Fixed Combination Prescription Drugs: FDA Policy”, Symposium on Combination Drugs, Washington, USA, 29. Nov. 1973

WHO Technical Report Series, No. 929, 2005

Annex 5
Guidelines for registration of fixed-dose combination medicinal products

Summary of requirements for the various scenarios

Requirement	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Rationale for the combination	Not usually	Not usually	√	√
Balancing advantages and disadvantages of the combination	Not usually	Not usually	√	√
Marketing status in other countries	√	√	√	√
Analysis of literature data in the submission	Possibly for pharmaceutical development	Possibly for pharmaceutical development	√	√
Pharmaceutical development studies	√	√	√	√
GMP certification of sites of manufacture	√	√	√	√
A full quality data set	√	√	√	√
Bioavailability data[a]	Not usually	Not usually	Sometimes	√
Bioequivalence data	√	√	Sometimes	Sometimes
Preclinical pharmacology and safety	Not usually	Not usually	Sometimes	√
Clinical safety and efficacy	Not usually	Not usually	√	√
Product information	√	√	√	√
Plan for passive post-marketing surveillance	√	√	√	√
Plan for active post-marketing surveillance	Not usually	Not usually	√	√

√ This is a requirement.

[a] Normally absolute bioavailability for a new chemical entity, or comparative bioavailability for a new dosage form.

Combination-Guideline EU I
Status quo

General Requirements (1): (according to the Directive 2001/83/EC*, Article 10, 1(b)):

"In the case of new medicinal products containing known constituents not hitherto used in combination for therapeutic purposes, the results of toxicological and pharmacological tests and of clinical trials relating to that combination must be provided, but it shall not be necessary to provide references relating to each individual constituent."

* of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

Combination-Guideline EU II
Status quo

General Requirements (2): (according to the Commission Directive 2003/63/EC*):

*"**5. Fixed Combination Medicinal Products:***

Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.

***For those applications a full dossier (Modules 1-5) shall be provided for the fixed combination medicinal product.** …"*

* of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (Annex I, Part II).

Combination-Guideline EU III
Status quo

Specific Requirements (1): (according to the CPMP NfG*):

- **Justify the particular combination of active substances**
- **Should be based on valid therapeutic principles**
- **Assess the potential advantages**
  - **improvement of the benefit/risk and/or**
  - **simplification of therapy**
- **against possible disadvantages**
  - **addition of different ADRs specific to each substance**

* Note for Guidance on Fixed Combination Medicinal Products CPMP/EWP/240/95

Combination-Guideline EU IV
Status quo

Specific Requirements (2):

- **Each substance of the fixed combination (FC) must have documented contribution within the combination ... to the claimed effect.**
- **Dose and proportion of each substance should be appropriate for the intended use.**
- **State if the claimed indication is**
  - **first-line (for patients receiving previously neither of the substances)**
  - **second-line (when monotherapy has not demonstrated a satisfactory benefit/risk ratio**
- **Clinical development ⇒ accordingly**

Combination-Guideline EU V
Status quo

Specific Requirements (3): Efficacy and Safety

- **For essentially new FC the data needed are similar to a new chemical entity in the situation where the FC is to be proposed (first or sec.-line).**
- **The proposed dose regimen must be justified.**
- **Confirmatory clinical trials are necessary to prove efficacy of the FC**
  - **preferably by parallel group design vs. its individual substances (and placebo when feasible)**
  - **comparative clinical studies of FC vs. reference might be necessary**
- **FC for long term use ⇒ safety data on 300-600 patients for 6 months or longer will be required.**

Tempora mutantur:

In addition, combination products have a perspective that is based on (outdated) pharmacological “expertise”: *The structure of a clinical study to demonstrate the therapeutic efficacy of an agent with more than three ingredients is so complicated that it is hardly ever performed.*

Potential place in therapy for single-pill triple combinations

Perhaps the greatest clinical benefit of single-pill combinations relative to multiple pills is the potential for improved adherence and the resulting improved control of hypertension.

Newly available single-pill triple combinations offer patients a well-tolerated and convenient option that can improve adherence to therapy. Notably, all three currently available triple combinations have demonstrated significantly better BP lowering compared with the component dual combinations.

Source: Management of hypertension with fixed-dose triple-combination treatments, Benjamin J. Epstein, Niren K. Shah and Nancy L. Borja-Hart, *Ther Adv Cardiovasc Dis* 2013 7: 246 originally published online 14 August 2013

European Medicines Agency

London, 19 February 2009
Doc. Ref. CHMP/EWP/240/95 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

GUIDELINE ON CLINICAL DEVELOPMENT OF FIXED COMBINATION MEDICINAL PRODUCTS

DISCUSSION IN THE EFFICACY WORKING PARTY	June – October 1994
TRANSMISSION TO THE CPMP	October 1994
TRANSMISSION TO INTERESTED PARTIES	October 1994
DEADLINE FOR COMMENTS	15 April 1995
RE-SUBMISSION TO THE EFFICACY WORKING PARTY	October 1995
RE-SUBMISSION TO THE CPMP	November 1995
RE-SUBMISSION TO THE EFFICACY WORKING PARTY	March 1996
RE-SUBMISSION TO THE CPMP	March 1996
APPROVAL BY THE CPMP	17 April 1996
DATE FOR COMING INTO OPERATION	17 October 1996
DRAFT REV. 1 AGREED BY EFFICACY WORKING PARTY	January 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION REV. 1	21 February 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 May 2008
REV. 1 AGREED BY EFFICACY WORKING PARTY	January 2009
ADOPTION BY CHMP	19 February 2009
DATE FOR COMING INTO EFFECT	1 September 2009

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 February 2013
EMA/CHMP/779887/2012
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need to revise the Guideline on the clinical development of fixed dose combinations of medicinal products regarding dossier content requirements

Fixed-combination medicinal products have been increasingly used either to improve compliance or to benefit from the added effects of the two medicinal products given together. The proposed combination should always be based on valid therapeutic principles. In addition, it is necessary to assess the potential advantages (e.g. product rapidly effective, higher efficacy or equal efficacy and better safety) in the clinical situation against possible disadvantages (e.g. cumulative toxicity), for each fixed combination product and for each dose of the fixed combination product.

Potential advantages may also include the counteracting by one substance of an adverse reaction produced by another one and the simplification of therapy.

Clinical developments should correspond to each situation/intended claim. In addition, particular attention should be drawn to the doses of each active substance in the fixed combination product. Each dose combination should be carefully justified and clinically relevant (e.g. in cases when each component of the fixed combination has several possible dosages, dosages that have shown benefit on hard clinical outcomes may be preferable for the fixed combination than the dosages effective on surrogate endpoints only).

Guideline concerning the scientific requirements for applications according to Article 10b of Directive 2001/83/EC, as amended, so-called 'fixed-combination' medicinal products. The scientific principles applicable to fixed-combination products will also be applied in the assessment of 'combination pack' medicinal products.

Combination packs would only be acceptable in very exceptional cases, when there would be clear public health benefits for the treatment regimen and/or compliance, taking into account the required justifications set-out in section 4.1 of this guideline. Applicants are therefore advised to consult with the relevant National Competent Authority/EMEA prior to submission, on the acceptability of the proposed combination pack.

The scientific principles set-out in this guideline are also applicable to a new chemical substance which dissociates in vivo into two well known active substances. A rationale should be given.

Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2013
Clinical Medical

Because existing developmental and regulatory pathways focus primarily on assessment of the safety and effectiveness of a single new investigational drug acting alone, or in combination with a previously approved drug, FDA believes guidance is needed to assist sponsors in the codevelopment of two or more new investigational drugs. Although interest in codevelopment has been most prominent in oncology and infectious disease settings, codevelopment also has potential application in other therapeutic settings. Therefore, this guidance is intended to describe a high-level, generally applicable approach to codevelopment of two or more new investigational drugs. It describes the criteria for determining when codevelopment is an appropriate option, makes recommendations about nonclinical and clinical development strategies, and addresses certain regulatory process issues.

Guidance for Industry

Botanical Drug Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2004

Copies of this Guidance are available from:

Botanical drug products that are derived from a single part of a plant (e.g., leaves, stems, roots, or seeds), or from a single species of alga or macroscopic fungus (e.g., a mushroom), are not considered to be fixed-combination drugs within the meaning of 21 CFR 300.50 and 330.10(a)(4)(iv). Consequently, they do not have to meet the requirements for combination drugs, principally the need to demonstrate that each component or active ingredient makes a contribution to claimed effects.

Botanical drugs composed of multiple parts of a single species of plant, alga, or macroscopic fungus, or of parts from different species of plants algae, or macroscopic fungi, currently are subject to the combination drug requirements. However, FDA is considering revising its regulations to allow for the exemption of such botanical drugs from application of the combination drug requirements under certain circumstances.

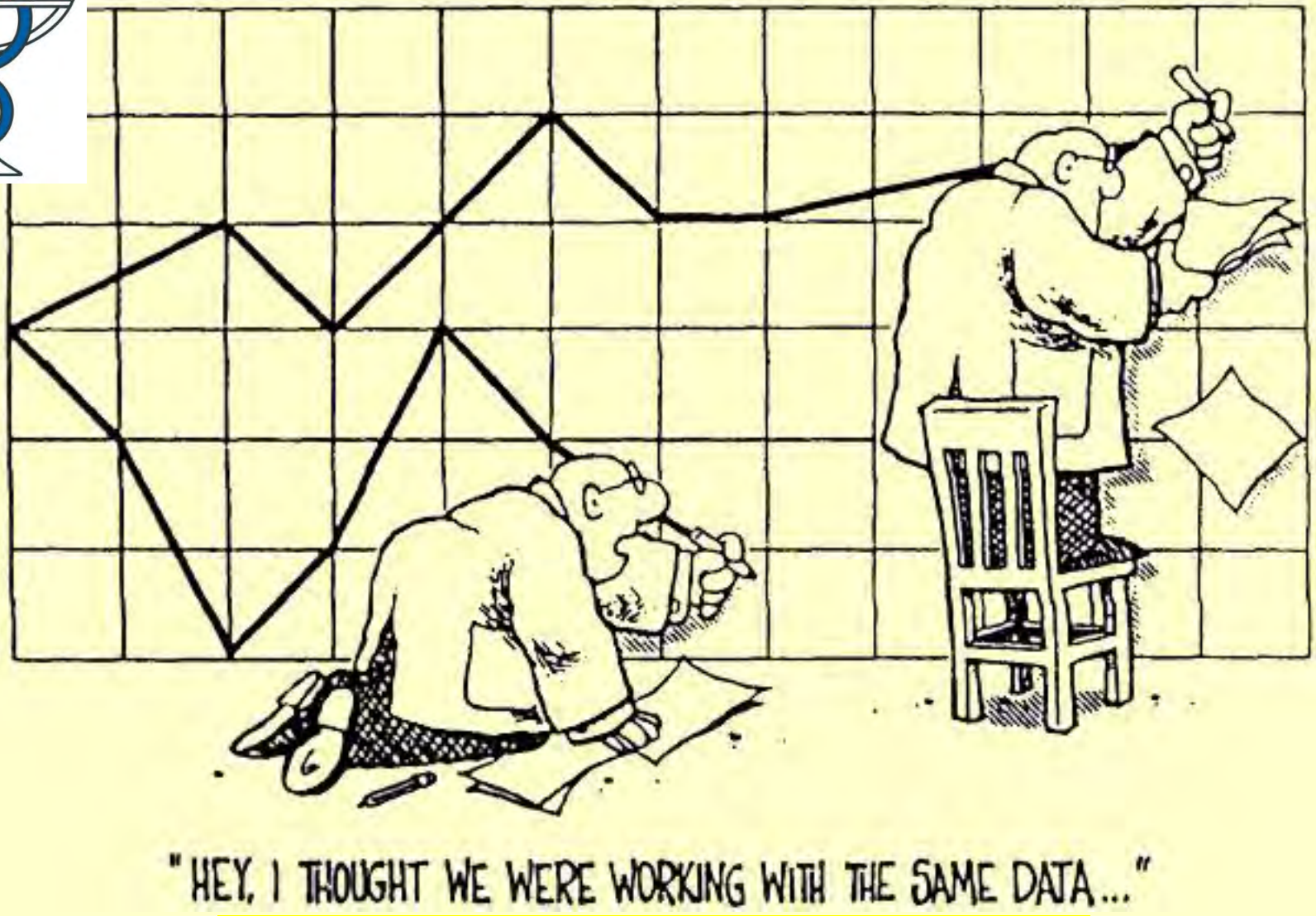
Our Vision I: Therapeutic Concepts

For several years, personalized medicine is on the rise. Patients benefit from successful treatment regimens based on their (genetic) needs. The increasing use of drug combinations for treatment shows the limits of the currently practiced single drug approval and offers new regulatory options: The approval of “therapeutic concepts”, a treatment regimen for a defined indication, which includes several medicines and diagnostics.

A therapeutic concept is the approval of a drug regime. This is not necessarily a fixed drug combination in a single pharmaceutical dosage form (fixed combination). The aim of the approval of therapeutic concepts should be, among other things, easy adjustable dosages of each medication to the patient.

Our Vision II: Therapeutic Concepts

- Approval of a treatment regimen consisting of two or more already on the market or not yet approved drugs for a specific indication and patient population, as well as, if necessary for the safe and effective use of the regime, the approval of a companion diagnostic. The drugs (and the companion diagnostic) should be developed and tested together for the purpose.



Thank You !

Killing with Nervo-Opt 1952

Der Vorgang soll sich so abgespielt haben: Der Verurteilte hat von einem Ärzteberater auf seinen Wunsch außer einem Beruhigungsmittel „Bonased" drei Schachteln des Medikaments „Nervo-Opt" erhalten.

Uncertain Murderer's Weapon.

Eric Mareo (44), on April 15, is charged with having murdered, by administering veronal tablets to his wife, Thelma Clarice.

Kenneth Massey Griffin, Government Analyst, said that the deceased's organs revealed veronal (Barbital, 5,5-diethylbarbituric acid). From the organs and bedclothes a total of 14.78 grains of veronal was extracted. Dr. Walter Gilmour, pathologist, said that the post-mortem indicated an over dose of a hypnotic drug. There was no disease, and the appendix was healthy. From the evidence given he concluded that death was due to veronal poisoning. The veronal extracted by the analyst indicated that Mrs. Mareo had a fatal dose. Witness estimated that she had probably at least 100 grains. Cross-examined, Dr. Gilmour said It was impossible to say whether the last veronal dose taken by Mrs. Mareo was in the milk given her on the Saturday night prior to her death on the Monday. Veronal was a drug used quite innocently by lay people. The giving by a layman of veronal to a relative or friend would not have the same significance as the giving of arsenic or strychnine. He thought, however, that the dangers of veronal were widely known. Deaths from veronal were usually due to misadventure. Suicide was a good second, but murder by veronal poisoning was rare. He did not know of any normal adult being so murdered. There was no recorded case but one or two suspected cases.

Counsel: There is a recorded case of ten grains killing a person? Witness: Yes, but that would not be due to veronal alone. There is a recorded case of a recovery from a dose of 360 grains? — That's so. It would be possible to administer 360 grains without fatal effects? — Yes, in some cases. Yet a dose of 50 grains might prove fatal? — Yes. So it is a very uncertain murderer's weapon? — Yes, it is. Witness said that a patient did not rouse from a fatal dose of veronal except in case of having pneumonia. It was possible that what might be a non-fatal dose for one person might be fatal to another in a highly nervous condition. The veronal group was unique hi this respect. Veronal could not be given in a tablet to a person without his know ledge, but it could be given as a powder in food or liquid if the person concerned were unsuspecting. Witness knew of no reason why veronal should not be given in milk. Milk hi such a case would curdle, and the veronal would then take longer to pass into the bloodstream. Witness believed that Mrs. Mareo had a dose early on Saturday and another dose half an hour before entering her final sleep. He believed that in all she must have had about 100 grains. Counsel referred to the fact that only a small quantity of veronal was recovered, but witness said it was possible for an analyst to recover completely the poison distributed in the bedclothes and mat tress. Witness said he did not know of a case of a person who had taken veronal showing signs of recovery and then lapsing into a fatal coma without further doses. He thought Mrs. Mareo would have recovered at the stage when she was given the milk even without medical treatment, provided she had been given the necessary food and fluids. Counsel: I suggest that veronal could not have been administered in the mill? Witness: If it is correct that she was slipping into coma when the milk was being administered, then the milk did not contain veronal. Witness, replying to a further question, said that veronal dissolved in sal volatile. The hearing was adjourned.

chemischen Befund bei der Obduktion als erwiesen an. Zu dieser Zeit war noch 1 gr. des Giftes Veronal nachweisbar.