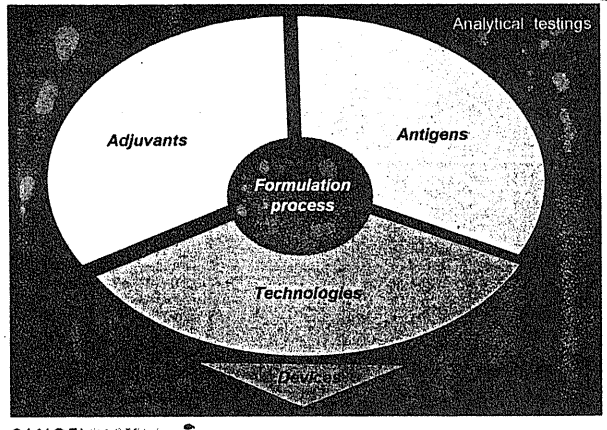
Vaccine Formulation Development



Alum vaccines – Physico chemical characterisation of Aluminium oxyhydroxide

What are the mineral adjuvants?

- Aluminium oxyhydroxide
  - AlOOH
    - Boehmite (France)
    - Goethite
  - Al(OH)3
    - Bayerite
    - Gibbsite
    - Nordstrandite
- Aluminium hydroxyphosphate
  - $Al(OH)_x(PO_4)_y$
- Calcium phosphate (no more used today)
  - $Ca(OH)_x(PO_4)_y$

Today, I will present results on Aluminium oxyhydroxide

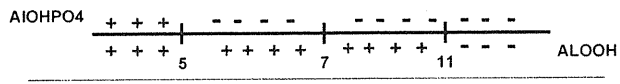
Vaccine & Adjuvants AlOOH / $AlOHPO_4$

- **ALOOH / $AlOHPO_4$**
- Adsorption At pH : 7 **Choose AlOOH for Antigens with IEP < 7**
  Choose $AlOHPO_4$ for Antigens with IEP > 7

  Needed or not , in regard to the antigens

- Donan Effect

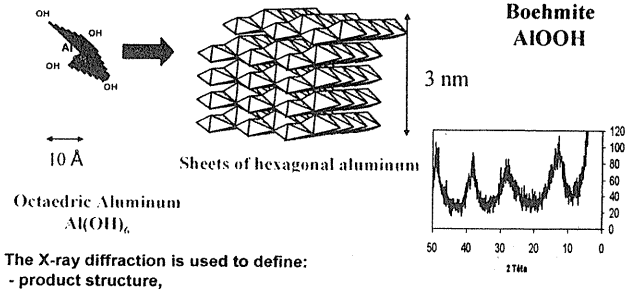
  Exp / $AlOHPO_4$ Buffer pH 7.0 ⟹ pH µenviron. : # 5.2



Characterization of Aluminum oxyhydroxide

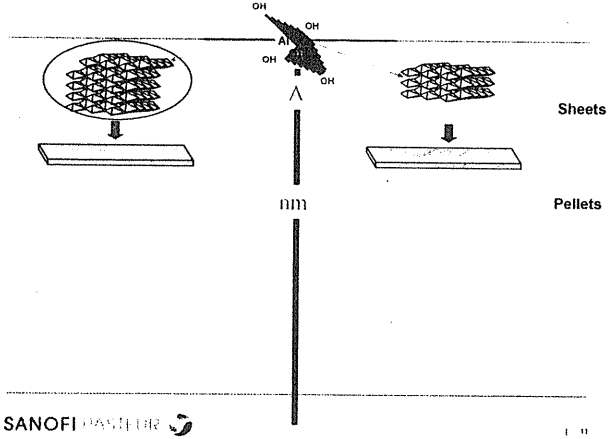
- Physico chemical Characterization
  - surface area measurements (Nitrogen adsorption BET)
  - Crystalline (X ray diffraction)
  - Particle size (Laser diffraction)
  - Viscosity
  - IPE (Zeta potential)
- Adsorption capacity with antigen
  - Tetanus
  - Diphtheria
- Activity on mice or guinea pig
  - Tetanus
  - Diphtheria

Structure of Aluminium oxyhydroxide by X-ray diffraction

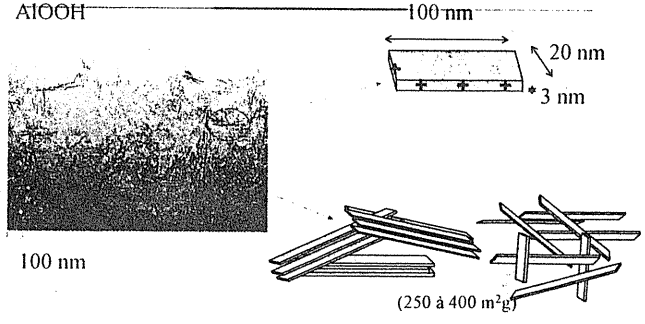


The X-ray diffraction is used to define:
- product structure,
- identify the form of thin aluminum compound
- define the level of crystallinity

Structure & texture of Aluminum oxyhydroxide



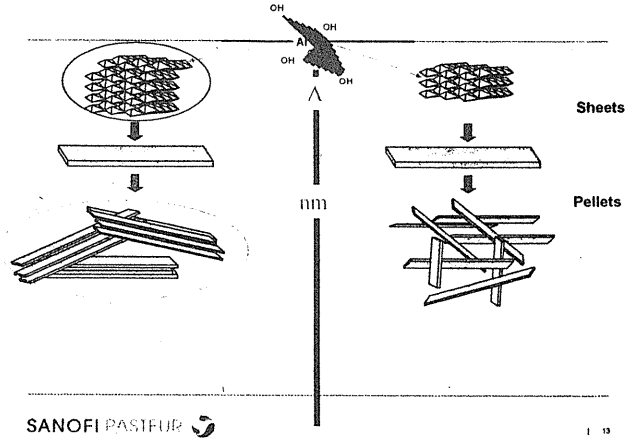
Texture of Amulinum oxyhydroxide by Cryo Microscopy (Cryo TEM) & Nitrogen adsorption



From Cryo microscopy, pellet size is determined.

From Surface area measurements , the texture of the pellet is determined

Structure & texture of Aluminum oxyhydroxide



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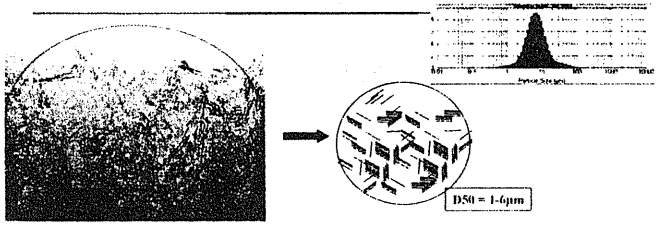
Texture of aluminum oxyhydroxide By laser diffraction



- The product is thixotropic.
- Pellets form aggregates linked by hydrogen bonds
- These aggregates are stable. Over time (after 3 years), the aggregate size increases slightly
- The dissolution of these aggregates is possible at pH = 2

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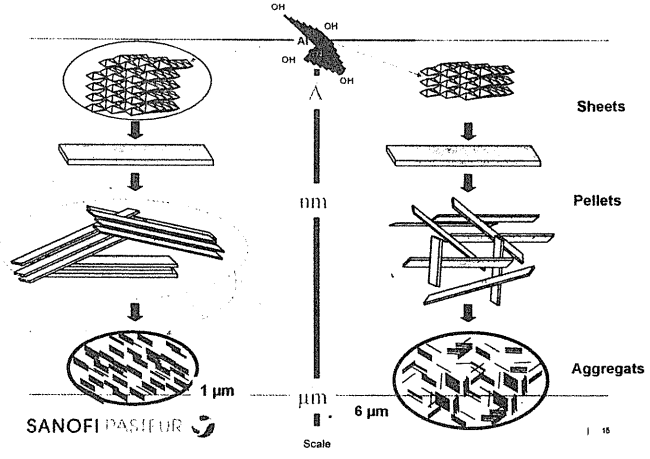
Structure & texture of Aluminum oxyhydroxide



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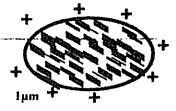
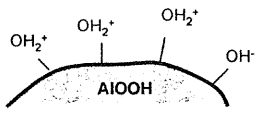
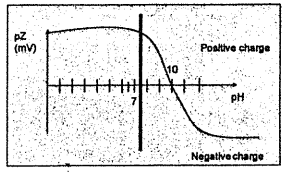
Surface Charge



- pH of vaccine are about 7
- At pH=7, surface charge of AlOOH is positive

PIE AlOOH = 10





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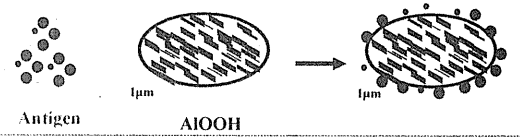
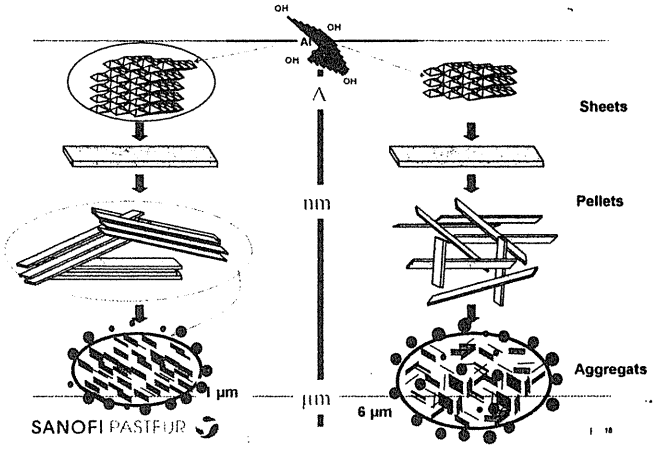
Adsorption of Antigen on aluminium adjuvant

Impact of antigen adsorption on adjuvant depend on
- Nature of antigen
- Surface charge of antigen and AlOOH
- Particle size of antigen and AlOOH
- Texture of AlOOH

Example : Protein size (160 KDa) is too large to enter into micropores of the gel. The adsorption of antigen occurs mostly at the surface of AlOOH aggregate



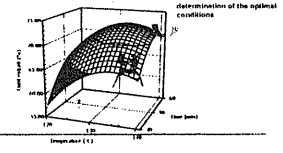
Structure & texture of Aluminum oxyhydroxide



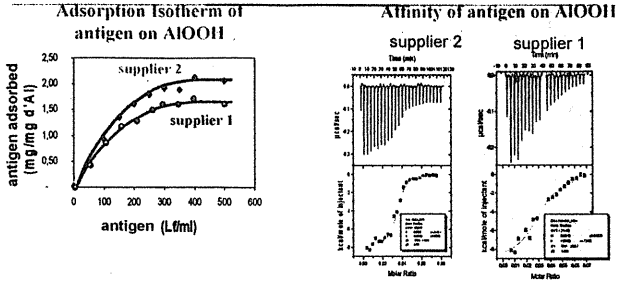
Alum vaccines – Physico chemical characterisation of the interface between AlOOH and Antigen

Analyse of adjuvant and antigen interactions

- Characterization by physico-chemistry
  - **Adsorption capacity,**
  - **Isothermal Titration Calorimetry**
- Modelisation of the adsorption capacity



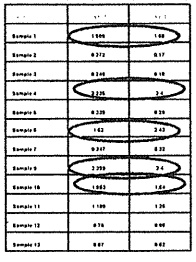
Adsorption capacity of the antigen on the adjuvant



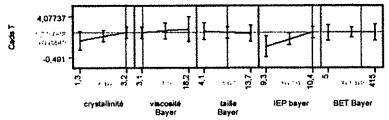
The adsorption capacity depend on adjuvant and antigen characteristics

Adsorption capacity of Tetanus & Diphtheria

- Based on Langmuir isotherm



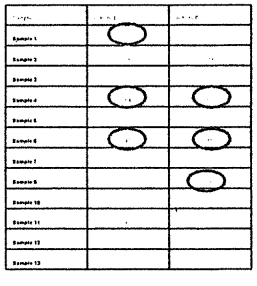
- Adsorption capacity of T & D were measured with several Aluminum adjuvant



Depending on physico-chemical characterization, the adsorption capacity goes from zero to high value (2.4 mg/mg Al)
The more the adjuvant crystallinity is low (high value of fwhm°), the more the adsorption capacity is high
The more the adjuvant IEP is high, the more the adsorption capacity is high

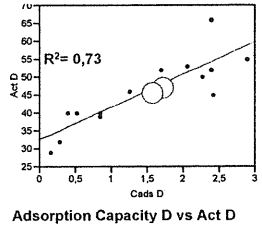
Activity of Tetanus & Diphtheria

- Different adjuvant samples (different characteristics) were formulated with Tetanus and Diphteria
- Activity of tetanus were measured on mice
  - Samples with low adsorption capacity had no activity
- Activity of diphtheria were measured on guinea pig

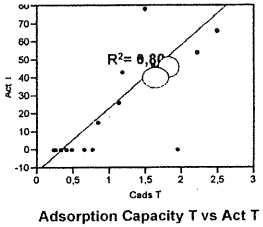


Depending on physico-chemical characteristic of the adjuvant, the activity for Tetanus and Diphteria vary from zero to high value in a DT vaccine

Relation between Adsorption capacity and Activity



Adsorption Capacity D vs Act D



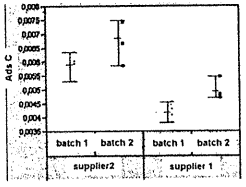
Adsorption Capacity T vs Act T

the more the adsorption capacity is high, the more the T & D activity is high

SP Supplier
SP Supplier

Influence of aluminium oxyhydroxide supplier and antigen batches on adsorption capacity

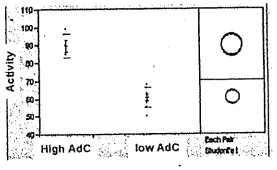
- The Tm and the particle size of the antigen has an impact on the adsorption capacity
- The structure of the gel has also an impact on adsorption capacity



The adsorption capacity may be predict by the quality of the antigen and mineral adjuvant

Influence of adsorption capacity (Ads C) on activity

- Analysis of different antigen batches adsorbed on one batch of one adjuvant



the more the adsorption capacity is high, the more the activity is high

Efficiency and Robustness

- To get robust and efficient product, formulation development have to take into account aluminum adjuvant and antigen characterization and interaction
- Aluminum adjuvant characterization is key to understand adsorption and non adsorption of antigen.
- The need of interaction characterization between adjuvant and antigen is key for efficiency and robustness of the multivalent vaccine.

Hexavalent vaccines – Formulation Process

Formulation Development
- Pre-Requisite -

Product knowledge

- Antigen Manufacturing / purity profile, pH, buffer, contaminants
- 1st stability data (/ bulk)
  - Supportive data for the process definition
  - Adsorption requited for stability or not
- Adjuvant ? & Interactions ?
- Concentration targeted range : Adjuvant and Antigen
- Administration route

Formulation Development

- **Excipients and conditions screening**
  - Optimal pH and buffer conditions
  - Optimal Excipient concentration

Avoid excipient from animal origin and not well characterized

- **Formulation optimization**
  - Adsorption
  - pH
  - Mixing order
- **Process optimization**
  - Mixing impact
  - Filling
  - Container impact

Vaccines & Excipients

If we observe an excipient effect (positive or negative) on the antigen stability, it can be due to its:

- Chemical properties
- Physical properties
- Structure
  - Eg :

$NH_2 - \underset{H}{\underset{|}{C}}(R_1) - R_2$ with R_1 = O or S, $R_2 = NH_2$ or linear chain (-O-C..., -COH , -NH-C , -C-C=C , -C-C- ..)

⟹ urea ($NH_2 - CO - NH_2$)

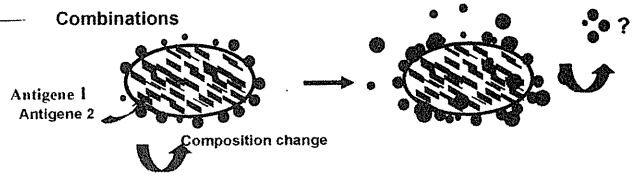
Hexavalents vaccines
Impact of adding order

Impact of antigen adsorption on adjuvant

Depending on antigen affinity for adjuvant

Desorption may occur that may affect efficacy

Combinations

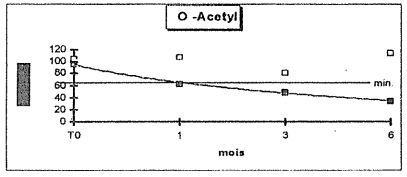


Optimization and Stabilization of Adsorption & Unadsorption

adsorbed / unadsorbed antigens
Stability issue - Polyoside

- Antigens : adsorbed & unadsorbed

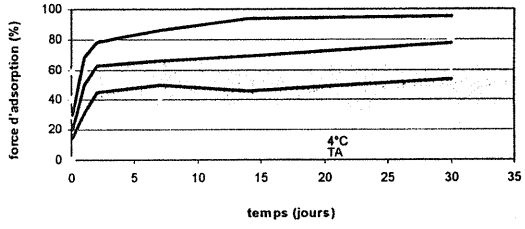
Exp. HA-Vi



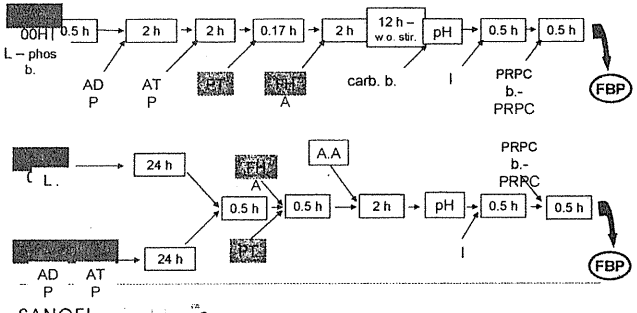
P1 // P2
Vi stability
at 25 ° C

Temperature effect on antigens adsorption

- adsorption force = f (time) at various temperatures

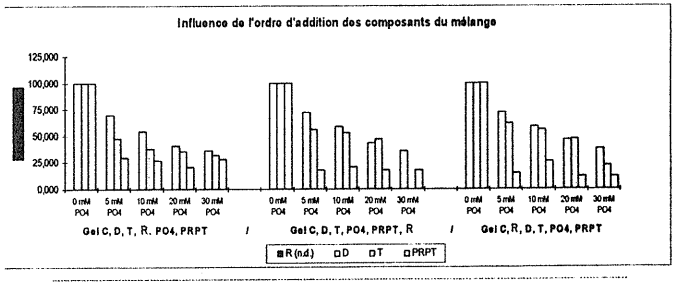


Stability / Compatibility
- Hexavalents vaccines :



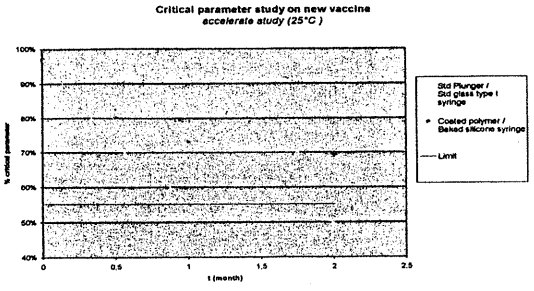
Impact of addition order

Addition order for : D , T , PO_4 & PRP-T ; Adsorption on $AlOHPO_4$



Interactions
Container Impact

- *Case of a New vaccine sensitive to free silicone and pH change*



- *Primary packaging effect is clearly seen on our critical parameter*

Hexavalent Vaccine Formulation

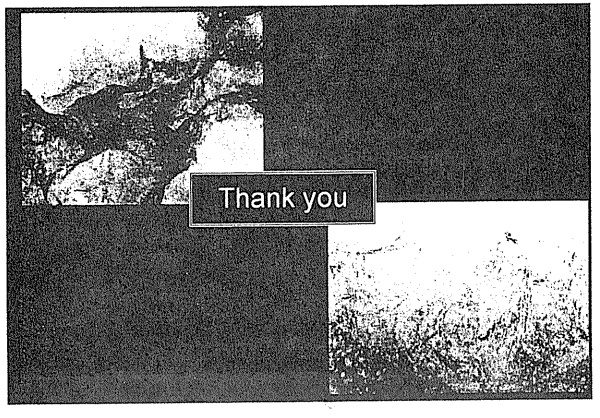
The vaccine formulation knowledge allow us to get a stable and complex balance between antigens & adjuvant.

Finally, hexavalent Vaccine formulation is a case by case development depending of the adjuvant and antigens characteristic

Vaccine Formulation need to be Controlled

Perspectives

- New technology is currently developed to :
  - **Facilitate stability**
  - **Prevent cold chain break**
  - **Prevent antigen adsorption**
  - **Develop multivalent vaccines with more than 6 antigens**
  - **Product multivalent as required by countries needs**



S2-2 US-licensed Acellular Pertussis Vaccines

William Egan (PharmaNet Consulting, former FDA CBER)

This presentation will discuss the various US-licensed acellular pertussis vaccines, including the acellular pertussis combination vaccines. The presentation will cover the recommended US immunization schedule for infants and children with an emphasis on how the various combination vaccines fit into that schedule. The presentation will provide the composition of the acellular pertussis vaccines regarding the particular pertussis components of the vaccines and the assays that used to determine vaccine potency. Finally, the aluminum adjuvant contents of the licensed acellular pertussis vaccines will be presented along with a discussion of current thoughts regarding the safety of the amount of aluminum that children may receive from the US-recommended infant immunization schedule.

US-licensed Acellular Pertussis Vaccines

William Egan, PhD

Former Deputy Director and Former Acting Director
Office of Vaccines Research and Review, CBER, FDA

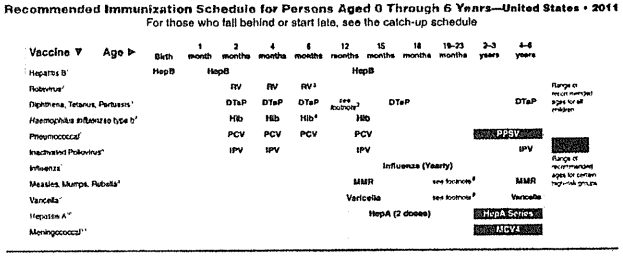
US Immunization Schedule for Selected Vaccines: ACIP Recommendations

- DTaP
  - 2, 4, and 6 months; 15 – 18 months; 4 – 6 years
  - The 4th dose may be administered as early as 12 months provided at least 6 months have elapsed since the 3rd dose
- Hepatitis B
  - Birth, 1 – 2 months, 6 – 12 months
  - Administration of 4 doses of HepB is permitted if a combination vaccine is used after the birth dose

US Immunization Schedule for Selected Vaccines: ACIP Recommendations

- IPV
  - 2, 4, 6 – 18 months; 4 – 6 years
  - If 4 or more doses are administered prior to 4 years of age, an additional dose should be administered at 4 – 6 years
- Hib conjugate
  - 2, 4, 6 months of age; 12 – 18 months
  - If PedVaxHib (PRP-OMP) or Comvax (RecombivaxHB, PedVaxHib) are administered at 2 and 4 months, a subsequent dose at 6 months is not indicated ; a booster dose at 12 – 15 months months is required for infants who complete the 2 dose schedule prior to 12 months

United States Pediatric Immunization Schedule: Advisory Committee on Immunization Practices



Current US-licensed Acellular Pertussis Vaccines

- Infanrix (GSK Biologics): D, T, aP (6 weeks to 7 years of age)
- Daptacel (Sanofi Pasteur, Ltd): D, T, aP (6 weeks to 7 years of age)
- Tripedia (Sanofi Pasteur, Inc): D, T, aP (6 weeks to 7 years of age)
  - (can be used to reconstitute ActHib → TriHIBit)
- Kinrix (GSK Biologics): D, T, aP, IPV (4 years to 7 years of age)
- Pediarix (GSK Biologics): D, T, aP, HepB, IPV (6 weeks to 7 years of age)
- Pentacel (Sanofi Pasteur, Ltd): D, T, aP, IPV, Hib (6 weeks to 5 years of age)

- Boostrix (GSK Biologics): T, d, ap (10 years of age and older)
- Adacel (Sanofi Pasteur, Inc): T, d, ap (11 to 65 years of age)

Pertussis Antigen Content of US-licensed Pertussis Vaccines

Vaccine	PT (μg)	Fim (types 2 and 3) (μg)	FHA (μg)	PRN (μg)
Infanrix	25	---	25	8
Daptacel	10	5	5	3
Tripedia*	23.4	---	23.4	---
Kinrix	25	---	25	8
Pediarix	25	---	25	8
Pentacel	20	5	20	3
Boostrix	8	---	8	2.5
Adacel	2.5	5	5	3

*Pertussis antigens produced by the Research Foundation for Microbial Diseases of Osaka University (BIKEN), Osaka, Japan

Potency Determination for US-licensed DTaP Vaccines

- "Diphtheria and tetanus toxoid potency is determined by measuring the amount of neutralizing antitoxin in previously immunized guinea pigs. The potency of the acellular pertussis components (PT, FHA, and pertactin) is determined by enzyme-linked immunosorbent assay (ELISA) on sera from previously immunized mice." — From the Infanrix package insert

- "Both diphtheria and tetanus toxoids induce at least 2 units of antitoxin per mL in the guinea pig potency test. The potency of the acellular pertussis vaccine components is determined by the antibody response of immunized mice to detoxified PT, FHA, PRN and FIM as measured by enzyme-linked immunosorbent assay (ELISA)." — From the Daptacel package insert

D and T Antigen and Aluminum Contents of US-licensed Pertussis Vaccines

Vaccine	D (Lf)	T (Lf)	Aluminum (mg)	Additional
Infanrix	25	10	≤ 0.625	
Daptacel	15	5	0.33	Contains 3.3 mg of 2-PE, not as a preservative
Tripedia	6.7	5	0.17	Contains trace thimerosal (< 0.3 μg Hg/dose)
Kinrix	25	10	≤ 0.6	
Pediarix	25	20	≤ 0.85	
Pentacel	15	5	0.33	
Boostrix	5	2.5	≤ 0.39	
Adacel	5	2	0.33	Contains 3.3 mg of 2-PE, not as a preservative

US-licensed Vaccines and Aluminum Content

- "The amount of aluminum in the recommended individual dose of a biological product shall not exceed:
  (1) 0.85 milligrams if determined by assay
  (2) 1.14 milligrams if determined by calculation on the basis of the amount of aluminum compound added;
  (3) 1.25 milligrams determined by assay provided that data demonstrating that the amount of aluminum used is safe and necessary to produce the intended effect are submitted to and approved by the Director, Center for Biologics Evaluation and Research." -- 21 CFR 610.15 (a)
- The "norm" has been that single doses do not exceed 0.85 mg of aluminum; dialysis patients may receive 1.0 mg of aluminum per dose of HepB vaccine.
- The CFR has recently been amended to allow exceptions.

US-licensed Vaccines and Aluminum Content

- Federal Register /Vol. 76, No. 71 /April 13, 2011 /p 20513
  "The final rule does not alter the existing requirements regarding the amount of aluminum in a biological product. Instead, in a change that is analogous to the one FDA issued in 1981, involving the groups who were at high risk of contracting hepatitis, the final rule allows either the Director of CBER or the Director of CDER to approve an exception or alternative when the Director determines that a biological product meets the requirements for safety, purity, and potency for the conditions for which the applicant is seeking approval, but contains an amount of aluminum that is higher than currently permitted by § 610.15."

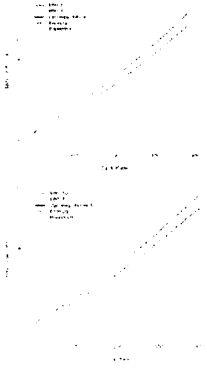
Aluminum Content and Vaccine Safety

- Concerns about the use of aluminum in vaccines in the late '90s prompted a Workshop, sponsored by the US National Vaccine Program Office, on aluminum in vaccines in May, 2000. The general use of aluminum salts in vaccines, as well as pharmacokinetic studies, were presented at the meeting [Keith LS, Jones DE, Chou CHJ. Aluminum Toxicokinetics Regarding Diet and Vaccinations. Vaccine, 20: S-13 – S17 (2002); Baylor NW, Egan W, and Richman P. Aluminum Salts in Vaccines – a US Perspective. Vaccine, 20: S34 – S39 (2002)]
- In their overall summary of the Workshop, Eickhoff and Meyers noted that "Based on 70 years of experience, the use of salts of aluminum as adjuvants in vaccines has proven safe and effective." [Eickhoff TC and Meyers M. Workshop Summary: Aluminum in Vaccines. Vaccine, 20: S1 – S4 (2002)]

Aluminum Content and Vaccine Safety

- According to a recent pharmacokinetic study by FDA, the risk to infants posed by the total aluminum exposure from the entire recommended series of vaccinations over the first year of life is extremely low. [Mitkus RJ, King DB, Hess MA, Forshee RA, Walderhaug MO, Updated Aluminum Pharmacokinetics Following Infant Exposures through Diet and Vaccination. Vaccine 29: 9538 – 9543 (2011)]
- These pharmacokinetic studies utilized updated parameters for
  - Current recommended vaccines for infants
  - Baseline aluminum levels at birth
  - Current data on how the body accumulates aluminum
  - Current information on aluminum elimination
  - More accurate information on how quickly aluminum spreads away from the site of injection
  - Current data on safety levels for aluminum in the body
  - Current information on infant weights
- The calculations were based on the maximal amount of aluminum that an infant could receive during the first year of life

Aluminum Content and Vaccine Safety



"Our results indicate that body burdens of following maximal exposure to aluminum adjuvant do not exceed those based on an accepted regulatory standard of safe aluminum levels, i.e., the MRL established by ATSDR."

MRL: Minimal Risk Levels
ATSDR: Agency for Toxic Substances and Disease Registry

Vaccine Additives and Residuals

For a listing of vaccine manufacturing additives and residuals, see:

TM Finn and W Egan, "*Vaccine additives and manufacturing residuals in United States-licensed vaccines*" in Vaccines, 5th ed., SA Plotkin, WA Orenstein, PA Offit, Eds., pp 73 – 81 (2008)

S2-3 わが国の DPT ワクチンの安全性と有効性

岩城正昭（国立感染症研究所　細菌第二部）

わが国において、薬事法 42 条第 1 項の規定に基づき「生物学的製剤基準」（生物基）が定められており、これに従ってワクチンの品質管理が行なわれている。
DPT 関連の（D、P、T のいずれかを成分として含む）ワクチンとして、生物基には 10 種類が収載されているが、実際に現在市場に流通しているのは 4 種類である。
これらのワクチンのうち、沈降精製百日せきジフテリア破傷風混合ワクチン(DTaP)と沈降ジフテリア破傷風混合トキソイド(DT)は現在国内 4 社から供給されており、沈降破傷風トキソイド(T)は 5 社、成人用沈降ジフテリアトキソイド(成人用 D)は 1 社から供給されている。今後、不活化ポリオワクチンを成分として加えた DTaP-IPV が導入されることが見込まれている。

わが国の現行の DPT 定期接種スケジュールは DTaP と DT により行なわれている。DTaP ワクチンは、百日せき成分として百日咳菌全菌体を用いていた DTwP に代わり、世界に先駆け 1981 年に導入された。現行の生物基の DTaP の規定は、そのときに作成されたものを現在も基本的に踏襲している。

一方、1990 年の WHO minimum requirement (Technical Report Series (TRS) 800 に収載)においては、DTaP としてではなく D と T のそれぞれの条文で性質が記載されており、わが国の生物基の記載と数値の異なる項目がみられる（力価、アルミニウム含量等）が、安全性と有効性について遜色がなければ、WHO と異なる基準を制定することは許容されている。

今回は、わが国の人口動態統計、伝染病統計、感染症発生動向調査、予防接種後健康状況調査、予防接種後副反応調査などに基づき、現行の DPT およびその関連ワクチンの安全性と有効性について論じる。

厚生労働省科学研究費補助金ﾚｷﾞｭﾗﾄﾘｰｻｲｴﾝｽ研究事業
「 医薬品を巡る環境の変化と生物学的製剤基準の在り方に関する研究 」シンポジウム
「国際化時代の生物学的製剤基準とワクチンの品質確保のありかた」

わが国のDPTワクチンの安全性と有効性

国立感染症研究所
細菌第二部
岩城正昭

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DPTワクチン(D、T部分)の現行基準について

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日本で現在使われているDPTおよび関連ワクチン

- DTaP(ads)(沈降精製百日せきジフテリア破傷風混合ワクチン)
- DT(ads)(沈降ジフテリア破傷風混合トキソイド)
- T(ads)(沈降破傷風トキソイド)
- 成人用D(ads)(成人用沈降ジフテリアトキソイド)
- (DTaP-IPV(ads) － 承認申請中)

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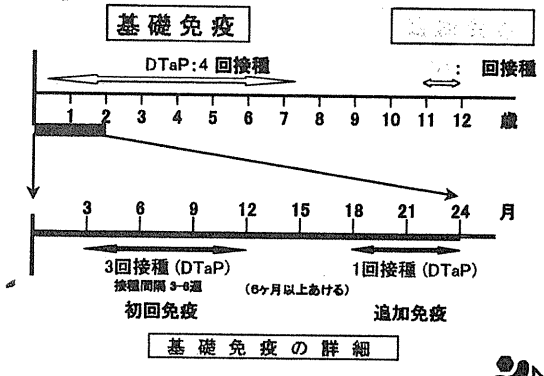
DPT関連のワクチンスケジュール



DTaP:精製沈降ジフテリア破傷風百日せき混合ワクチン
DT:沈降ジフテリア破傷風混合トキソイド

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日本の生物学的製剤基準

(昭和24年(1949年)の百日咳ワクチン基準制定された後各種ワクチン、血液製剤等の基準が個別に制定されてきた)

・昭和46年(1971年)7月17日　厚生省告示第263号により公示

・昭和60年(1985年)10月2日　改正(厚生省告示第159号)

・平成5年(1993年)10月1日　改正(厚生省告示第217号)

・平成16年(2004年)3月31日　改正(厚生労働省告示第155号)

D、T関連ワクチンの国内基準

ワクチン	力価	アルミニウム含量
沈降DTaP	47 U/mL (D), 27 U/mL (T)	0.3 mg/mL
沈降DT	70 IU/mL (D), 40 IU/mL (T)	1.0 mg/mL
沈降T	40 IU/mL (T)	0.5 mg/mL
成人用沈降D	15 IU/mL (D)	1.0 mg/mL

DPTワクチンの基準(D、T関連)

	D力価	D抗原量	D抗原純度	T力価	T抗原量	T抗原純度	アルミニウム含量	ホルムアルデヒド含量
日本	47単位/mL以上	50 Lf/mLを越えない	1500 Lf/mgpN以上	27単位/mL以上	20 Lf/mLを越えない	1500 Lf/mgpN以上	0.3mg/mL以下	0.01 w/v%以下
WHO/EP	not less than 30 IU/SHD (60 IU/mL)	shall not exceed 30 Lf/SHD (60 Lf/mL)	(WHO) not less than 1500 Lf/mgpN	not less than 40 IU/SHD (80 IU/mL)	shall not exceed 25/SHD (50 Lf/mL)	(WHO) not less than 1000 Lf/mgpN	shall not exceed 1.25mg/SHD (2.5 mg/mL)	not more than 0.2g/L (0.02%)
中国	not less than 30 IU/SHD (60 IU/mL)	25 Lf/mL		not less than 40 IU/SHD (80 IU/mL)	7 Lf/mL		1.0 – 1.5 mg/mL	not more than 0.2g/L (0.02%)

DPTワクチンの基準(D、T関連)

	D力価	D抗原量	D抗原純度	T力価	T抗原量	T抗原純度	アルミニウム含量	ホルムアルデヒド含量
日本	47単位/mL以上	50 Lf/mLを越えない	1500 Lf/mgpN以上	27単位/mL以上	20 Lf/mLを越えない	1500 Lf/mgpN以上	0.3mg/mL以下	0.01 w/v%以下
WHO/EP	not less than 30 IU/SHD (60 IU/mL)	shall not exceed 30 Lf/SHD (60 Lf/mL)	(WHO) not less than 1500 Lf/mgpN	not less than 40 IU/SHD (80 IU/mL)	shall not exceed 25/SHD (50 Lf/mL)	(WHO) not less than 1000 Lf/mgpN	shall not exceed 1.25mg/SHD (2.5 mg/mL)	not more than 0.2g/L (0.02%)
中国	not less than 30 IU/SHD (60 IU/mL)	25 Lf/mL		not less than 40 IU/SHD (80 IU/mL)	7 Lf/mL		1.0 – 1.5 mg/mL	not more than 0.2g/L (0.02%)

アルミニウムアジュバントと安全性に関して

Baylor et al. (2002) Vaccine 20, S18–S23 "Aluminum adjuvants have a demonstrated safety profile of over six decades; however, these adjuvants have been associated with severe local reactions such as erythema, subcutaneous nodules and contact hypersensitivity."

Thesten et al. (2005) Vaccine 23, 1515–1521 "A total of 647 subjects were enrolled. 224 (35%) received a dTpa formulation with 0.5 mg aluminium, 208 (32%) a formulation with 0.3 mg aluminium and 214 (33%) a formulation with 0.133 mg aluminium.(略)No clear difference between study groups in local or general side effects was demonstrated."

Jefferson et al. (2004) Lancet Infect. Dis. 4, 84-90 "In young children, vaccines with aluminium hydroxide caused significantly more erythema and induration than plain vaccines (odds ratio 1·67 [95% CI 1·57–2·24]) and significantly fewer reactions of all types (0·21 [0·15–0·28]). The frequencies of local reactions of all types, collapse or convulsions, and persistent crying or screaming did not differ between the two cohorts of the trials. In older children, there was no association between exposure to aluminiumcontaining vaccines and onset of (local) induration, swelling, or a raised temperature, but there was an association with local pain lasting up to 14 days (2·05 [1·25–3·38]). We found no evidence that aluminium salts in vaccines cause any serious or long-lasting adverse events. Despite a lack of good-quality evidence we do not recommend that any further research on this topic is undertaken."

Knuf et al. (2006) Vaccine 24, 5627-5636 "In the first study phase, DTaP with no aluminum induced the highest frequency of ETS and fever. All other candidate vaccines caused lower rates of local and general reactions than the reference DTaP."

Kataoka et al. (2009) Vaccine 27, 1881-1888 "When injecting into mouse footpad, rabbit back skin and mouse quadriceps muscle, the imported vaccines induced much severer inflammation and tissue injury comparing to Japanese DTaPs irrespective of animal species, injection site and injection volume suggesting that these vaccines may induce stronger local reactogenicity."

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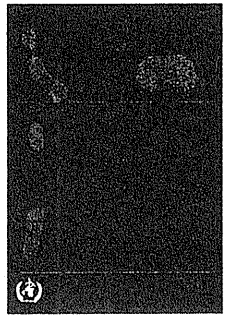
WHO requirements (TRS800, 1990)の考え方



TRS800 p93, p111

"If national requirements differ from these requirements, it is recommended that the former should be shown to ensure that the vaccine is at least as safe and as potent as that prepared in accordance with the requirements formulated below."

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日本における患者数と副反応

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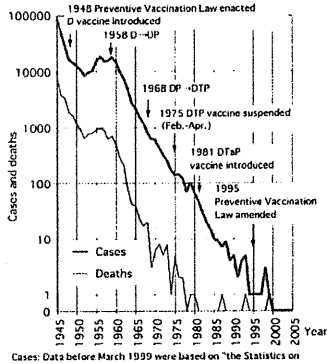
Figure 1. Incidence of diphtheria in Japan, 1945-2005



Cases: Data before March 1999 were based on "the Statistics on Communicable Diseases in Japan".
Data after April 1999 were based on the National Epidemiological Surveillance of Infectious Diseases.
Deaths: Vital Statistics of Japan (Ministry of Health, Labour and Welfare)

IASR

IASR 27: 331-332; December, 2006

S2-4 ワクチン評価に関する制度と科学

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現在のワクチンの安全性、有効性の評価は、基本的に臨床試験に基づくこととなっている。かつて Behring が北里と行った 1901 年の第一回ノーベル賞受賞研究により、破傷風の抗毒素療法が確立した。これは、破傷風が中毒性疾患であり、毒素の中和により治療が可能との事実に基づく。抗毒素等の有効性（力価）の評価は、安全性や倫理的な制約から臨床的に行うのは困難であるが、基本的には毒素に感受性を示す動物で可能である。また全菌百日せきワクチンの有効性は、1945-1956 年のイギリス医学研究委員会の大規模な臨床試験で、免疫マウスの脳内攻撃試験で測定可能であることが確認され、全菌百日せきワクチンの有効性評価は、この力価試験により行われてきている。ワクチンの場合、治療薬と異なり、有効なワクチンの普及により疾病の流行はなくなり、臨床的有効性評価が困難になる。従って、このような実験室での有効性評価モデルなしには、新規ワクチン開発や既存製品の製法変更に困難を来すことになる。

臨床試験は、対象集団全体のワクチンに対する反応性から有効性や安全性を評価するために行う。しかし無作為に選択した偏りのない対象者を試験に組み込むことは、実際的にも倫理的にも無理がある。従って厳密な層別化による群別で複数のワクチンの相対比較は可能であるが、絶対的な安全性や有効性の評価は困難である。すなわち有効性や安全性の臨床評価結果は、対象者の母集団分布からの偏りにより試験毎に結果が異なる可能性が排除できない。

ワクチンに必要なのは防御免疫原性のみであり、防御に無関係の生物活性は不要な反応の原因となる可能性がある。実際には各種サイトカインの誘導を含め、防御に無関係の活性あるいは反応を特定するのは容易ではない。特に病原体成分には TLR 刺激等を介してサイトカイン誘導やアジュバント活性を示すものがあるが、こうした活性も安全性の観点からの制御が必要であり、少なくともワクチンのあらゆる生物活性の検索と定量法の確立が必要である。臨床的副反応と相関する生物活性の特定により、その管理に基づく副反応の制御が可能となる。臨床評価用ロットと同様の製造法で恒常的に製造することで、臨床評価結果により製品ロットの有効性、安全性が担保できると考えられており、GMP による製造の恒常性確認が必要となる。ただしこの方法が有効であるためには、有効な臨床評価とワクチン品質に直結した品質規格設定が前提となる。実例を用いて、現状の問題点と対応を検討してみたい。

Regulations and scientific bases for vaccine evaluation

Yoshinobu Horiuchi, Ph.D.
Ex-Chief, Lab. Pertussis and Endotoxin Control,
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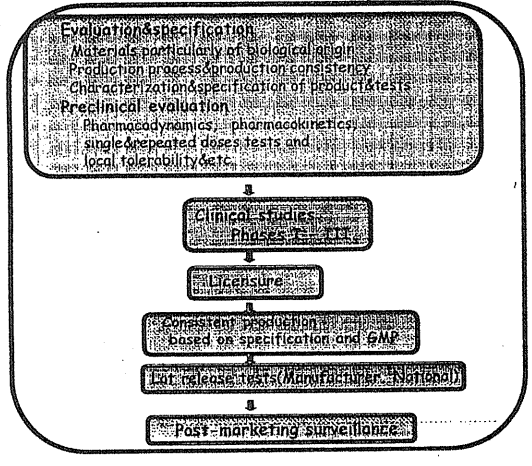
Disclaimer

This presentation is based only on my personal scientific views but not reflecting official views of any institutions

General vaccine evaluation system



Production procedures for split flu vaccines

1) Purified virion (inactivated?) ➡ Ether treatment
➡ Water soluble fraction ➡ Protein fraction rich in HA and NA

2) Purified virion (inactivated?)
➡ DOC or STDC treatment
➡ Split virion ➡ Fraction containing whole virus components
Used for formulating Arepanrix or Fluvax

(Summary Basis of Decision (SBD) AREPANRIX™ H1N1 AS03-Adjuvanted H1N1 Pandemic Influenza Vaccine, Health Canada), (Fluvax® vaccine 2011 (TT50-3839) Data sheet October 2010)