ERA Annual Conference on EU Law in the Pharmaceutical Sector

Current liability issues in the life sciences sector

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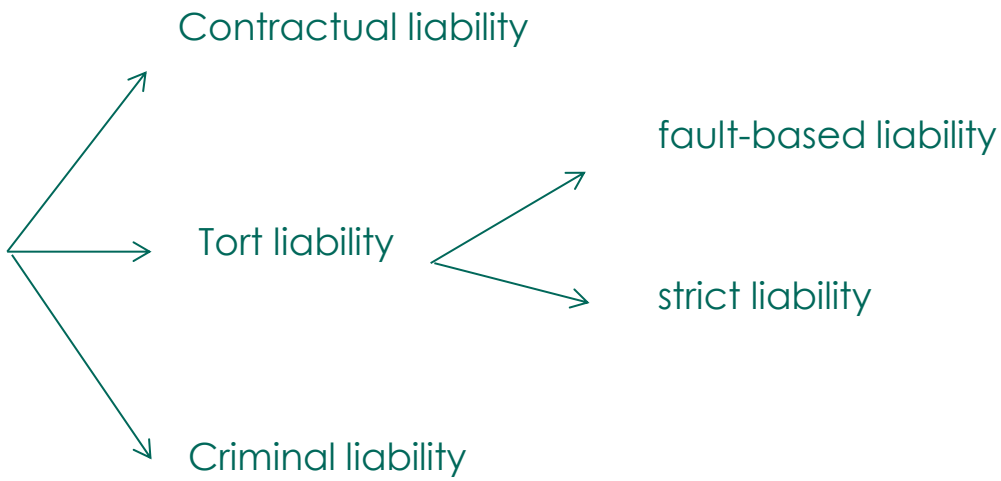
Reminder of legal principles

- Types of liability



- Possible parallel application of liability regimes

Liability for medicinal products | General

- **Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use (the "Community Code")**
- Actors
  - Manufacturer
  - Marketing authorisation holder
  - Distributor
  - Importer
  - [HCP, pharmacist, patient]
- Some relevant provisions of the Community Code:

Article 25
"Authorisation shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorisation holder."

Article 47a (2)
"Manufacturing authorisation holders, including those performing the activities referred to in paragraph 1 of this Article [i.e., removing or covering safety features]*, shall be regarded as producers and therefore held liable for damages in the cases and under the conditions set forth in Directive 85/374/EEC."*

Article 61 (4)
"The fact that the competent authority does not refuse a marketing authorisation pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer and the marketing authorisation holder."

Liability for medical devices | General

- **Directive 93/42/EEC of 14 June 1993 concerning medical devices (the "MDD")**
- **Directive 90/385/EEC of 20 June 1990 on active implantable medical devices (the "AIMDD")**
- **Directive 98/79/EC of 27 October 1998 on in vitro diagnostic medical devices (the "IVDMD")**
- Actors
  - Manufacturer
  - Authorised representative
  - Notified body
  - Distributor
  - Importer
  - [HCP, pharmacist, patient]

- No specific provisions on liability in the MDD, AIMDD or IVDMD
- Only reference to liability: Annex XI (6) to the MDD: "*The* [notified body] *must take out civil liability insurance, unless liability is assumed by the State under domestic legislation or the Member State itself carries out the inspections directly.*"
- Impact of **Regulation (EU) 2017/745 of 5 April 2017 on medical devices (the "MDR") and Regulation (EU) 2017/746 of 5 April 2017 on in vitro diagnostic medical devices (the "IVDMDR")** on liability

Life sciences: a liability minefield

- Research/Discovery (e.g. R&D licensing contracts)
- Development (e.g. clinical trial contracts; regulatory compliance; product liability for study drug)
- Manufacturing (e.g. contracts with toll manufacturers; GMP compliance)
- Marketing (e.g. outsourcing contracts for medical reps; unlawful promotion by reps; Anti-Bribery Act; incorrect instructions by technical reps)
- Distribution (e.g. contracts with wholesalers-distributors; GDP compliance)
- Surveillance (e.g. regulatory compliance; product liability)

→ Regular overlap between contractual, tort and criminal liability

→ Rise in liability cases due, *inter alia*, to globalisation of manufacturing process/supply chain and increased patient access to information

Product liability | Legal framework 1

- **Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products (the "PLD")**
  - Seeks to achieve complete harmonisation in matters regulated by it (ECJ, Case C-183/00, María Victoria González Sánchez v. Medicina Asturiana SA, paragraphs 23-33; ECJ, Case C-154/00, Commission v. Hellenic Republic, paragraph 20)
  - PLD and regulatory framework on pharmaceuticals apply simultaneously (Article 25 of Directive 2001/83/EC; Article 15 of Regulation 726/2004)
  - System of strict (= no fault) liability
  - Product: "*all movables even if incorporated into another movable or into an immovable*", including electricity. Includes medicinal products
  - Producer:
    - → Manufacturer of a finished product or of a component part
    - → Producer of any raw material
    - → Any person presenting himself as product's producer by putting his name, trade mark or other distinguishing feature on product
    - → Any person importing a product into European Economic Area for sale, hire, leasing or any form of distribution in course of his business
    - → If producer cannot be identified: each supplier of product, unless supplier informs injured person, within a reasonable time, of identity of producer or of person who supplied him with product
    - → If an imported product does not indicate identity of importer: each supplier of product, even if name of producer is indicated

Product liability | Legal framework 2

- Article 6 (1) PLD: "*A product is defective if it does not provide the safety which a person is entitled to expect taking all circumstances into account, including: (a) the presentation of the product; (b) the use to which it could reasonably be expected that the product would be put; (c) the time when the product was put into circulation*"
- Defectiveness is to be determined objectively by reference to a "*consumer expectation test*"
- A medicinal product can be defective in broadly four different ways
  - → Design defect
  - → Information or instruction defect (cf. Dutch Supreme Court, 30 June 1989, Halcion)
  - → Manufacturing defect
  - → Packaging defect
- Damage caused by death or by personal injury
- Damage to, or destruction of, any property other than defective product itself, with a lower threshold of EUR 500, provided that property:
  - → Is ordinarily intended for private use or consumption; and
  - → Was used by injured person mainly for his/her own private use or consumption

Product liability | Legal framework 3

- Injured person carries the burden of proof (damage, defect, causal link)
- Who is liable?
  - → "Cascade" system (See, notion of "producer")
  - → Exemptions (Article 7 PLD), incl. development risk defence and regulatory compliance defence
- Dual statute of limitations
  - → 3 years
  - → 10 years
- Not possible to exclude or restrict liability
- Scope of producer's liability:
  - → Article 8(1) PLD: "*Without prejudice to the provisions of national law concerning the right of contribution or recourse, the liability of the producer shall not be reduced when the damage is caused both by a defect in the product and by the act or omission of a third party*"
  - → Article 8(2) PLD: "*The liability of the producer may be reduced or disallowed when, having regard to all the circumstances, the damage is caused both by a defect in the product and by the fault of the injured person or any person for whom the injured person is responsible*"
- EC Consultation on the rules on producer liability for damage caused by a defective product (2017)

Product liability | Lessons from past case law

- **Case C-310/13, 20 November 2014, *Novo Nordisk Pharma GmbH v S*** (medicinal products)
  - **ECJ:** PLD cannot be interpreted as precluding a special liability system for the purposes of Article 13 under which the consumer has the right to require the manufacturer of the medicinal product to provide him with information on the adverse effects of that product

- **Case C-495/10 , 21 December 2011, *Centre hospitalier universitaire de Besançon v. Thomas Dutrueux, Caisse primaire d'assurance maladie du Jura*** (medical devices)
  - **ECJ:** PLD does not prevent national rules which provide for the strict liability of a service provider for the use of defective products
  - Comments:
    - PLD seeks to achieve complete harmonisation but only in matters regulated by it
    - National laws can be stricter or broader than the PLD

Product liability | Recent case law | Medicines

❖ **Case C-621/15, 21 June 2017, *N. W and Others v Sanofi Pasteur MSD SNC and Others***

- Victim seeking compensation from Sanofi Pasteur for damage allegedly suffered because of allegedly defective vaccines manufactured by it, but with no medical evidence to substantiate this claim
- Questions: Does PLD preclude relying on serious, specific and consistent circumstantial evidence to establish defect and causal relationship in the absence of scientific evidence? Does PLD preclude a presumption that causality is automatically established when pre-determined factual evidence is presented?
- **ECJ**: Sphere of liability for defective products not exhaustively harmonised by PLD beyond the matters regulated by it
  - Requiring certain and irrefutable medical evidence is contrary to the PLD
  - Circumstantial evidence possible, but must be serious, specific and consistent
  - Pre-determined facts automatically establishing causality not allowed
- Comments:
  - No medical evidence required → dangerous precedent?
  - Caveat: only when scientific evidence neither confirms nor rules out causality

Product liability | Recent case law | Medical devices

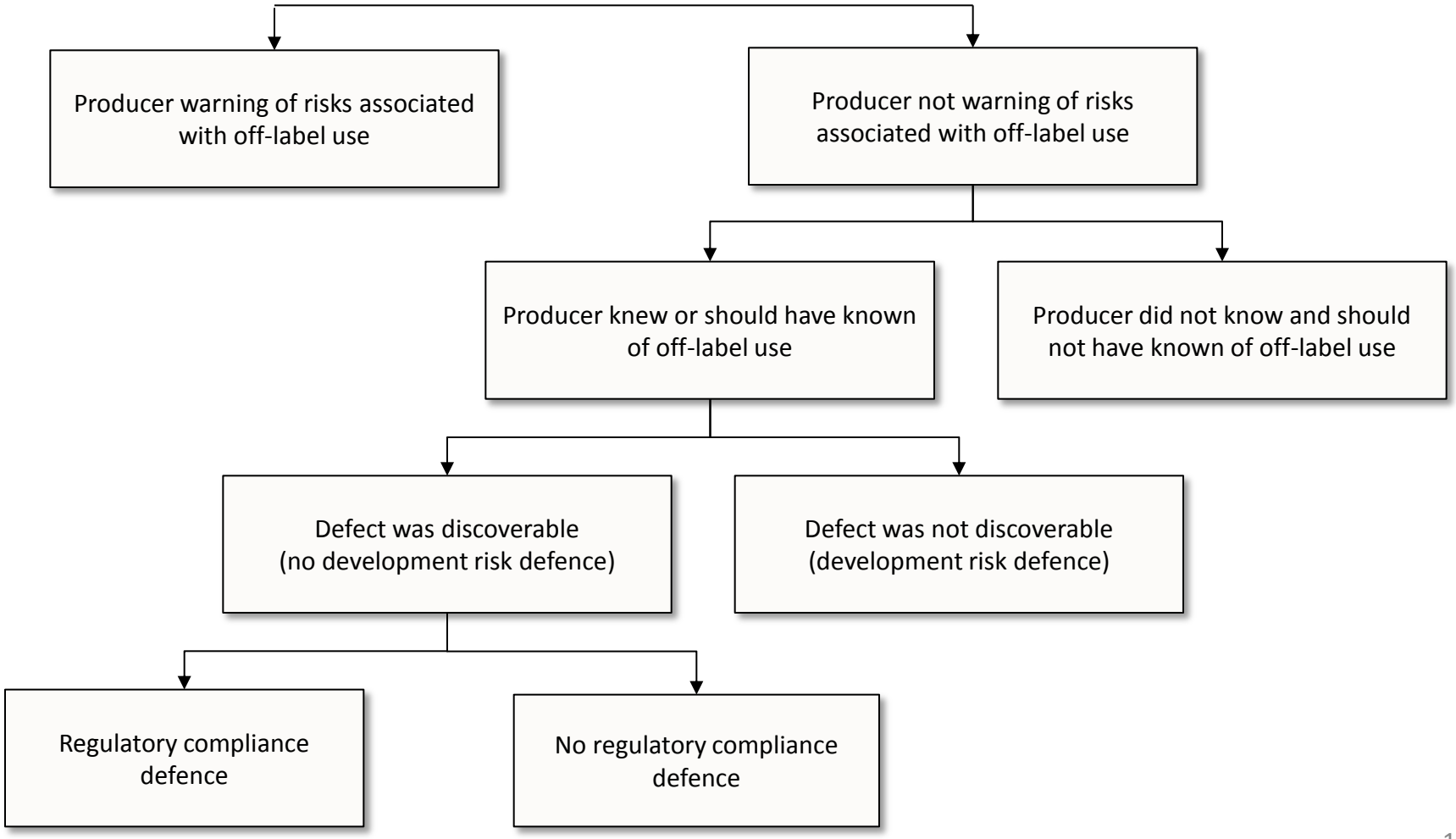
❖ **Joined cases C-503/13 and C-504/13, 5 March 2015, *Boston Scientific Medizintechnik GmbH v AOK Sachsen-Anhalt — Die Gesundheitskasse and Betriebskrankenkasse RWE***

- Health insurance companies seeking compensation for costs relating to implantation of pacemakers and defibrillators that had to be replaced after the manufacturer's quality control system had shown that the functioning of some might be affected
- Questions: Is a medical device defective if it belongs to a product group with a significantly increased risk of failure, but a defect has not been detected in this one specific device? Do costs to remove/replace the product constitute *damage caused by personal injury*?
- **ECJ**: Art. 6 PLD: defect when product does not provide the safety one is entitled to expect
  - Particularly vulnerable situation of patients using pacemakers/defibrillators
  - Potential defect in group: all products can be classified as defective
  - Compensation for damage = *all that is necessary* to eliminate harmful consequences
- Comments:
  - Batch liability: broad language changes burden of proof under LPD and can lead to unacceptable outcomes
  - Manufacturers likely to try to limit exposure through supply of information on risks

Other topical liability issues in life sciences sector | Off-label use

- Off-label use - Factors
- Marketing authorisation holder ("MAH") has not investigated and tested all potential applications of product
  - Tests and clinical trials are expensive + outcome is uncertain
  - Focus on one aspect of product to speed up marketing
  - Benefits of registration do not outweigh costs
  - Ethical, legal and/or practical reasons make clinical trials more complicated or not feasible
  - MAH not aware of feasibility to apply active substance for a specific treatment
- MAH has investigated and tested a specific application of product but decides against registering it
  - Avoid (product) liability claims
  - No incentive to register application
    - → No additional sales because product is already being used for application (albeit off-label)
    - → Different medicinal product of same producer is indicated for same application
- Off-label use may be induced by government
- October 2012: European Commission started "reflection process" with EU Member States regarding off-label use → "Study on Off-Label Use of Medicinal Products in the European Union" (Marjolein Weerda et al; Feb 2017)

Other topical liability issues in life sciences sector | Off-label use



First hypothesis: producer warning of risks associated with off-label use

- Likelihood of producer incurring liability under PLD decreases as consumer is better informed of product's risks (cf. information/instruction defect)
- Advisable to mention all possible side effects, including those relating to off-label use, in SmPC and package leaflet
- (↔ some case law, e.g., Paris Court of Appeals, 18 March 2004, Case 2002/15121, *Mr. and Ms. Verdet v. Sanofi-Synthélabo France and Others)*
- Caveat: even a warning of side effects (or a contra-indication) will not automatically and necessarily make product safe and discharge producer of any liability
  - Article 12 PLD: "*The liability of the producer arising from this Directive may not, in relation to the injured person, be limited or excluded by a provision limiting his liability or exempting him from liability*"

Second hypothesis: producer not warning of risks associated with off-label use

- Producer in principle liable (Article 6(1)(b) PLD)
- (Required) knowledge can, for instance, follow from fact that off-label use:
  - Is publicly known
  - Takes place on large scale
  - Is extensively documented
  - Accounts for significant percentage of product's sales
  - Was reasonably foreseeable

Second hypothesis: producer not warning of risks associated with off-label use

First sub-hypothesis: producer knew or should have known of off-label use

- Is any off-label use to be considered reasonably foreseeable? – Impact of 2010 pharmacovigilance revision
  - Directive 2010/84/EU broadened the definition of an "adverse reaction" in Article 1(11) of Directive 2001/83/EC, which now reads as follows: "*A response to a medicinal product which is noxious and unintended*"

    Recital 5 of Directive 2010/84/EU: goal was "*to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product*"

    → Adverse reactions that result from off-label use should also be reported
  - Article 23(2), indent 2 of Directive 2001/83/EC and Article 16(2), indent 2 of Regulation 726/2004: Requirement for MAH to report any new information which might influence the evaluation of the benefits and risks of the medicinal product, "*including both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation*")

Second hypothesis: producer not warning of risks associated with off-label use

First sub-hypothesis: producer knew or should have known of off-label use

- Is any off-label use to be considered reasonably foreseeable? – Impact of 2010 pharmacovigilance revision
  - Article 116 of Directive 2001/83/EC (suspension, revocation or variation of marketing authorisation when risk-benefit balance "*is not favourable*" – previously: "*is not positive under the normal conditions of use*")
  - EMA Work Programme 2013: Strategic objective 3.2 (Post-authorisation follow-up) includes "*[i]ncreasing the collection of information from 'real-life' use of medicinal products, including off-label use, through work within the ENCePP framework, and the use of inhouse data sources to better integrate the assessment of benefits and risks*"

Second hypothesis: producer not warning of risks associated with off-label use

First sub-hypothesis: producer knew or should have known of off-label use

- Development risk defence
  - Article 7(e) PLD
  - State of scientific and technical knowledge at time when producer put product into circulation was not such as to enable defect to be discovered
    - → To be interpreted strictly (ECJ, Case C-203/99, *Henning Veedfald v. Århus Amtskommune*, paragraph 15; ECJ, Case C-127/04, *Declan O'Byrne v. Sanofi Pasteur MSD Ltd and Sanofi Pasteur SA*, paragraph 25)
    - → Availability is determined by objective and general state of scientific and technical knowledge (ECJ, 29 May 1997, Case C-300/95, *Commission v. United Kingdom*, paragraph 29)
    - → Not available in all EU Member States (*e.g.*, not available in Finland and Luxembourg)
- If development risk defence is invoked successfully: no liability (*e.g.*, Amsterdam District Court, 3 February 1999, *Scholten v. Stichting Sanquin Bloed*voorziening)

Second hypothesis: producer not warning of risks associated with off-label use

First sub-hypothesis: producer knew or should have known of off-label use

- If development risk defence is not invoked successfully
  - Producer in principle liable
  - Escape liability on basis of regulatory compliance defence?
    - → Article 7(d) PLD
    - → (Information) defect must be due to compliance of product with mandatory regulations issued by public authorities
    - → Would seem available if producer can show that:
      - (i) he requested competent authorities to insert a warning (or contra-indication) in SmPC and/or package leaflet, and
      - (ii) authorities refused to approve insertion

Second hypothesis: producer not warning of risks associated with off-label use

First sub-hypothesis: producer knew or should have known of off-label use

- Escape liability on basis of regulatory compliance defence?

  → EMA guidance of 21 January 2013 on how to prepare and review SmPCs:

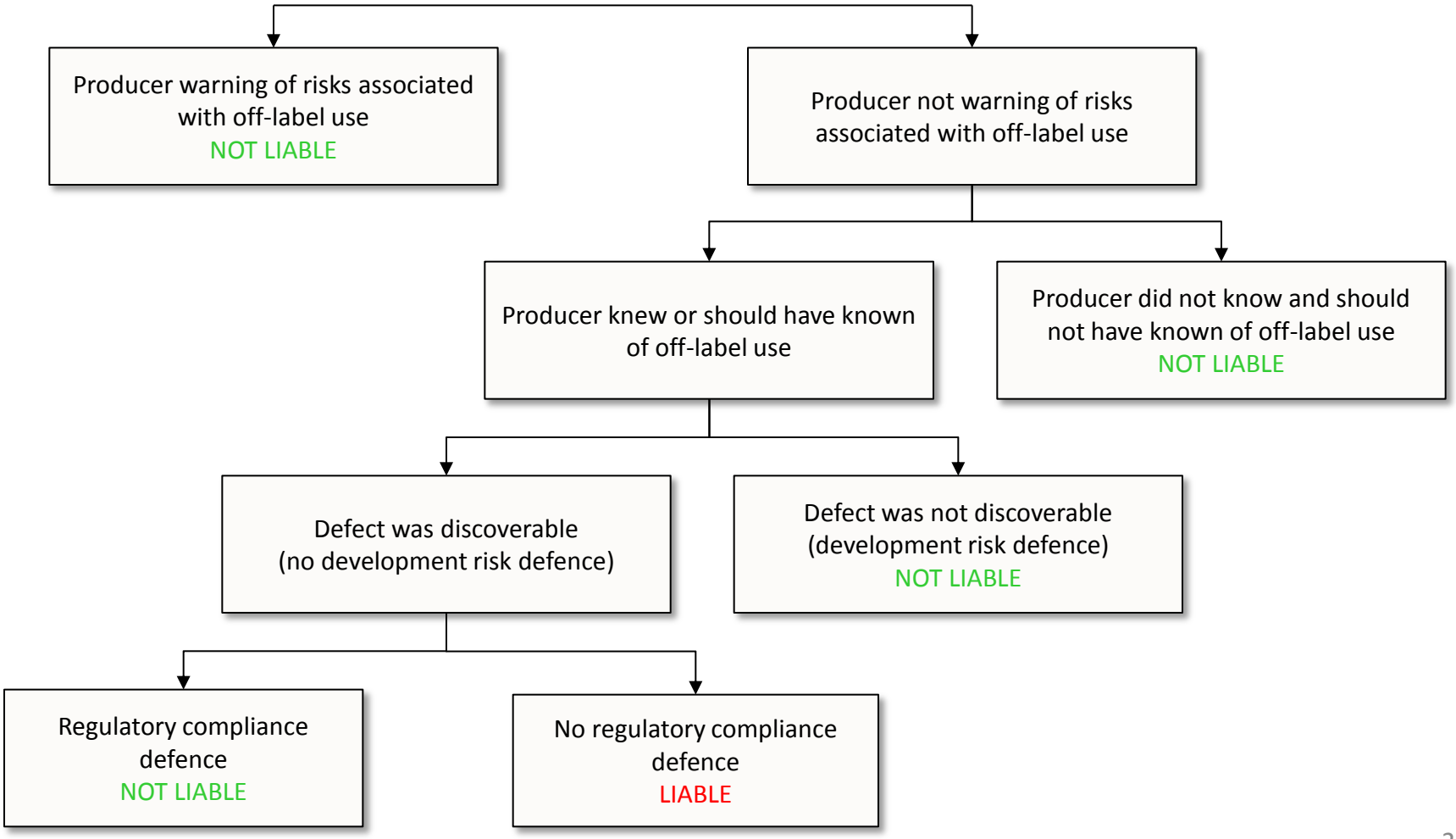
  - In principle, information on non-approved use is not expected in SmPC (with exception of data in paediatric population)
  - In accordance with *Guideline on Summary of Product Characteristics (SmPC)* of September 2009 (*See*, Notice to Applicants, volume 2C), information on a specific risk observed in off-label use should be provided in section 4.4 (Special warnings and precautions for use) of SmPC when it consists of a serious adverse reaction to which health care professionals need to be alerted

Second hypothesis: producer not warning of risks associated with off-label use

Second sub-hypothesis: producer did not know and should not have known of off-label use

- Producer not liable
- Physicians/patients have no obligation to inform MAH of off-label prescription/use
- Physicians often do not even realise that they are prescribing off-label

Product liability in case of off-label use - Summary



Liability of prescribing physician

- Prescribing physician is first avenue for redress
- Civil liability
  - Liable for negligence if physician did not act in accordance with standard of good medical care (*i.e.*, level of care that an average reasonable physician would have provided when placed in same situation)
  - Patient should prove:
    → Fault/negligence on part of physician
    → Damage (injury)
    → Causal link between damage and fault/negligence
  - No impact on liability of producer (Article 8(1) PLD)
- Criminal liability
- Disciplinary sanctions

Liability of pharmacist

- General professional liability, including for off-label medication:
  - Ensure that patients receive safe, effective and appropriate medication, with minimal risk
  - Advise patients properly on how to use the medication supplied
- Potential liability under PLD (*e.g.*, magistral preparation)

Other topical liability issues in life sciences sector | Miscellaneous (1)

❖ **Case C-219/15, 16 February 2017, *Elisabeth Schmitt v TÜV Rheinland LGA Products GmbH***

- Elisabeth Schmitt, victim of the PIP scandal, seeking damages from TÜV Rheinland, the notified body ("NB") responsible for the conformity assessment, for harm caused by defective breast implants sold by PIP
- Questions: NBs required to carry out unannounced inspections, examine devices and examine business records? Does a failure of a NB to comply with its obligations give rise to liability vis-à-vis end users of MDs?
- **ECJ**: degree of discretion/no general obligation, but duty to act with all due diligence
  - If indications that MD does not comply with MDD: duty to take necessary steps to fulfill obligations under MDD
  - MDD does not govern conditions under which a NB is liable vis-à-vis the end users in case of a culpable infringement of its obligations
  - Product Liability Directive (Directive 85/374/EEC) does not preclude application of other systems of contractual or non-contractual liability, such as fault → Liability of a NB governed by national law
- Comments:
  - NBs may be liable for faulty MDs
  - No EU-wide answer to the liability question → how will liability be applied by national courts?

Other topical liability issues in life sciences sector | Miscellaneous (2)

- Software
  - Case C-329/16, 7 December 2017, *Snitem and Philips France*
    - → Boundary of liability between software manufacturer and HCP?

- 3-D printing
  - Devices created by 3-D printers can qualify as medical devices (custom-made medical devices)
    - → Boundary of liability between 3-D printer manufacturer, HCP and service provider?

    3-D printing

- Worrying trend in US: "Innovator liability" argument: invoked to hold originator liable for injuries allegedly caused by ingestion of generic versions of his product. Threat to innovation.

Questions

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