Evaluating the effects of Draft Regulatory Guidance on Generic Drug Production Manufacturing - Ezetimibe and Beta lactams

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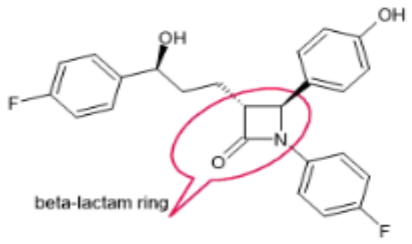
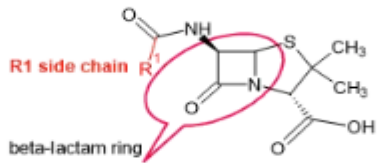
Upfront Summary

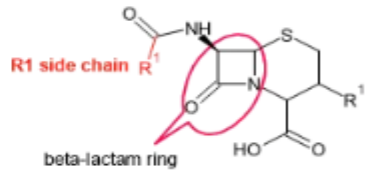
- FDA, EMA & others require highly sensitizing compounds, such as beta lactams, to be made in dedicated facilities due to the inability to set “acceptable daily exposures” based on allergenic effects
- In 2022, FDA issued a draft update to its beta lactam guidance and included ezetimibe, suggesting that it must be made in a dedicated facility
- Ezetimibe: cholesterol lowering drug on the market since 2002
  - Chemical structure has beta lactam ring
  - Data suggests
    - Doesn’t cause beta lactam type allergy
    - Presents an “exceedingly low” risk of hypersensitivity
- FDA inspectors are now issuing observations at sites producing ezetimibe-containing products on/in non-dedicated equipment/facilities
  - Worst case outcome: 3/2025 Glenmark recalled 23 drugs/148 lots



Ezetimibe



Penicillin



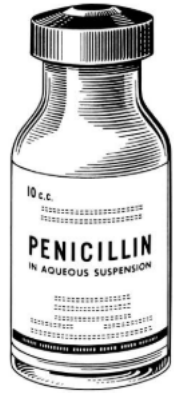
Cephalosporin

https://qvents.in/concerns-of-beta-lactam-contamination-triggers-massive-recall-by-glenmark/

Overview

- Antibiotic Beta lactams
- Regulatory history of beta lactams
- Toxicology and Clinica Data on Ezetimibe

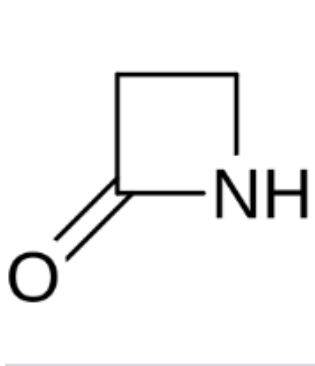
Antibiotic Beta lactams



- FDA, EMA, & PIC/S Require Beta lactams to be made in dedicated facilities
  - Began with focus only on antibiotics

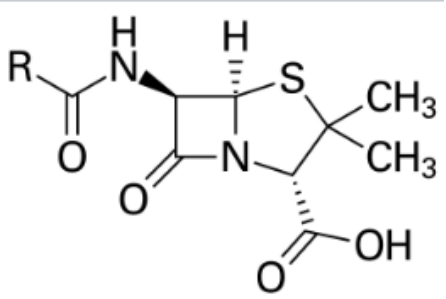
- FDA allows Beta lactams from the same class to be made at the same facility (FDA 2013, 2022)
  - Pencillins (e.g., ampicillin, oxacillin)
  - Cephalosporins (e.g., cephalexin, cefaclor)
  - Penems (e.g., imipenem, ertapenem)
  - Monobactams (e.g., aztreonam)

- Usually most up-to-date guidance matters, with beta lactams all matter



2-Azetidinone, the simplest β-lactam

PIC/S = Pharmaceutical Inspection Cooperative Scheme (56 regulatory authorities from 38 countries)

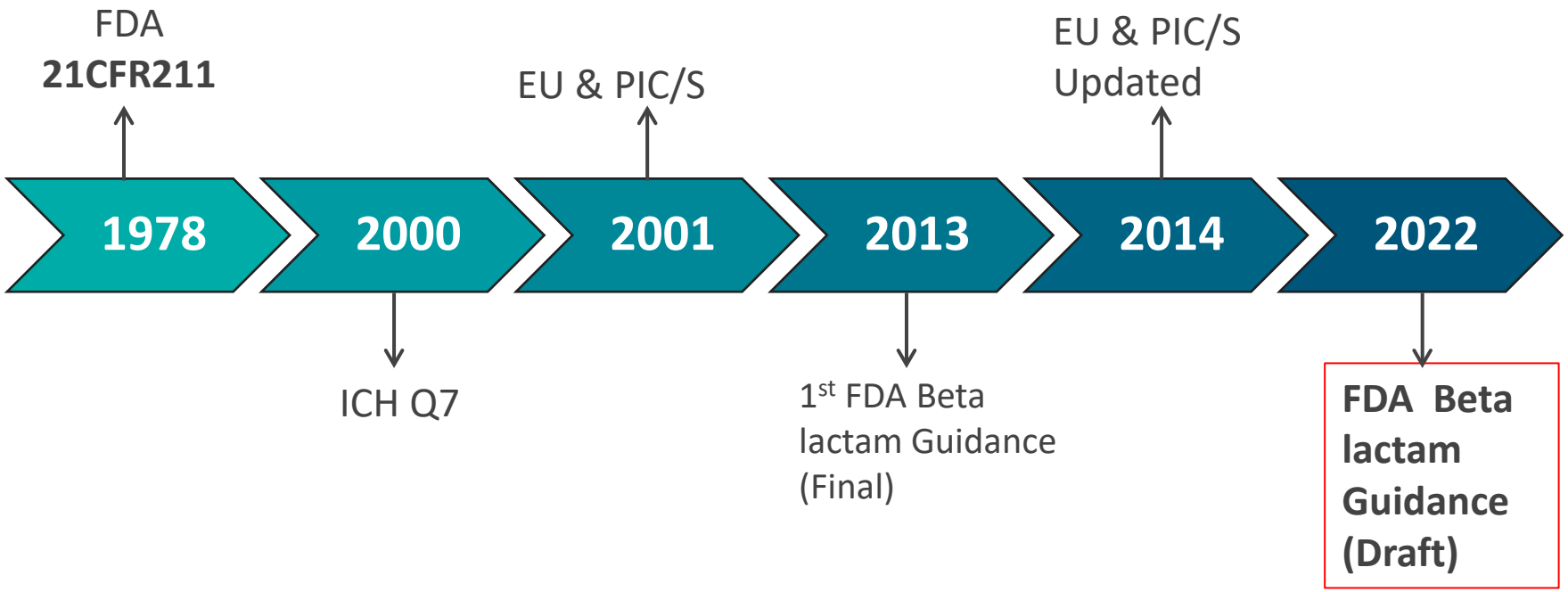


Penicillin core structure

Images: https://en.wikipedia.org/wiki/%CE%92-Lactam

Regulatory History: Where did beta lactam segregation begin?

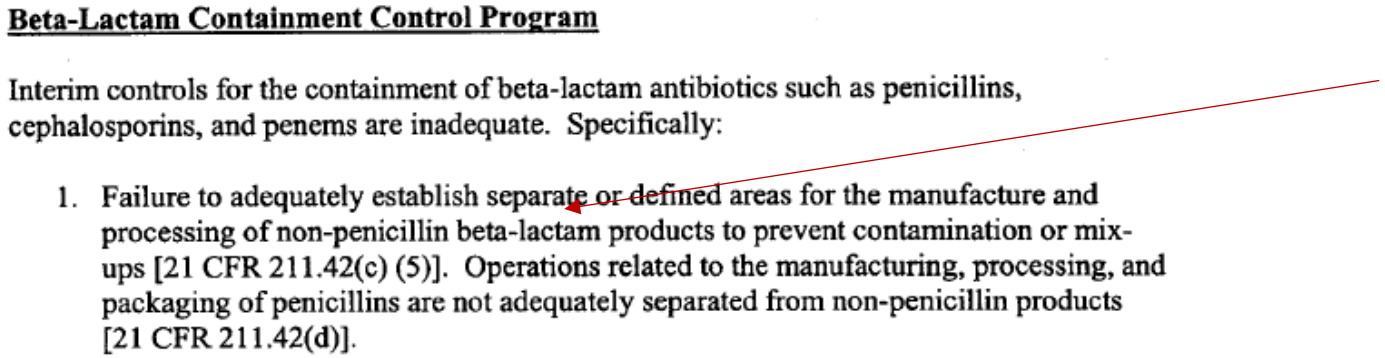
- Segregation of beta lactams dates to 1978 in the US and 2000/2001 elsewhere
  - Initial focus: Penicillin > Other beta lactam antibiotics > beta lactam compounds



CFR = Code of Federal Regulations
ICH = International Conference on Harmonization
PIC/S = Pharmaceutical Inspection Cooperative Scheme (56 regulatory authorities from 38 countries)

Beta Lactam Regulatory History
Guidance versus regulatory expectations – 2008 Warning letter Example

- Since the first requirements in 1978, the main change to guidance is to ***specify*** that requirements apply beyond just penicillin
- Text of 2008 warning letter (Ranbaxv):



Beta-Lactam Containment Control Program

Interim controls for the containment of beta-lactam antibiotics such as penicillins, cephalosporins, and penems are inadequate. Specifically:

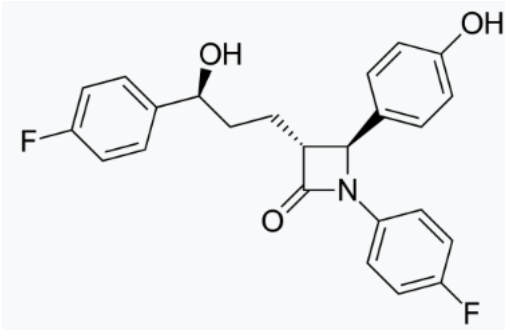
1. Failure to adequately establish separate or defined areas for the manufacture and processing of non-penicillin beta-lactam products to prevent contamination or mix-ups [21 CFR 211.42(c) (5)]. Operations related to the manufacturing, processing, and packaging of penicillins are not adequately separated from non-penicillin products [21 CFR 211.42(d)].

- **21CFR211.42(d)**
  - *"(d) Operations relating to the manufacture, processing, and packing of **penicillin** shall be performed in facilities separate from those used for other drug products for human use."*
  - Significance: Even before FDA's 2013 guidance, FDA expected beta lactam segregation

- Big change: 2022 FDA Draft Beta Lactam guidance included ezetimibe, a non-antibiotic beta lactam

Ezetimibe Pharmacology & Toxicology

Ezetimibe



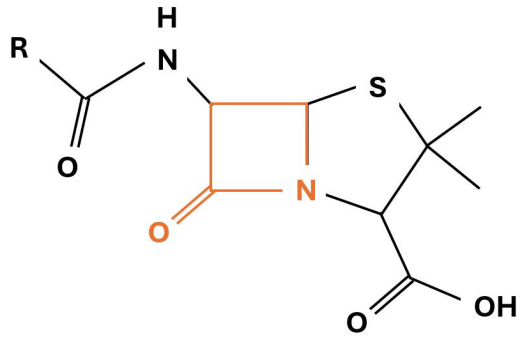
- Important cholesterol lowering drug for patients:
  - ***Important for patients***
    - who can't take statins such as: Atorvastatin, simvastatin, and others
    - who need greater cholesterol reduction than statins alone, Combination products: Simvastatin/ezetimibe Rosuvastatin/ezetimibe
  - ***Cost effective for patients***
    - Inhibitor medications.: limit small intestine's ability to absorb cholesterol from food or help liver absorb more LDL cholesterol (PCSK9 inhibitors). 30-Day USA cost comparison https://www.webmd.com/cholesterol-management/cost-high-cholesterol (6/2025):
    - Alirocumab (Praluent): $371.70 ($111.51 copay)
    - Evolucumab (Repatha): $476.64 ($142.99 copay)
    - Ezetimibe (Zetia): $9.26 ($2.78 copay)

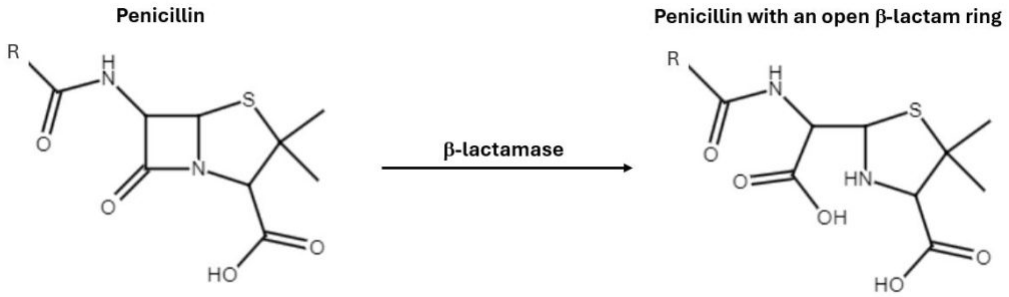
Do trace levels of carry over of Ezetimibe present a beta lactam type risk?

- **FDA Ezetimibe label** has ***no warnings or contraindications*** related to beta lactam hypersensitivity (last updated FDA, 7/2023)
  - Patients with penicillin or other beta lactam allergies ***can take*** ezetimibe
  - Only those allergic to ezetimibe can't take
- No cases of hypersensitivity were reported in ezetimibe ***clinical*** studies with >31,000 patients (Pradhan et al., 2020, Savarese et al., 2015)
  - Clinical studies have controlled exposures
  - Adverse events data show no trends and lower levels of allergic response than statins and beta lactam antibiotics
- ***Pre-clinical*** (animal) studies found no sensitizing potential (Japan, 2007)
- ***Mechanistic data*** explain lack of beta lactam-hypersensitivity (next slide)

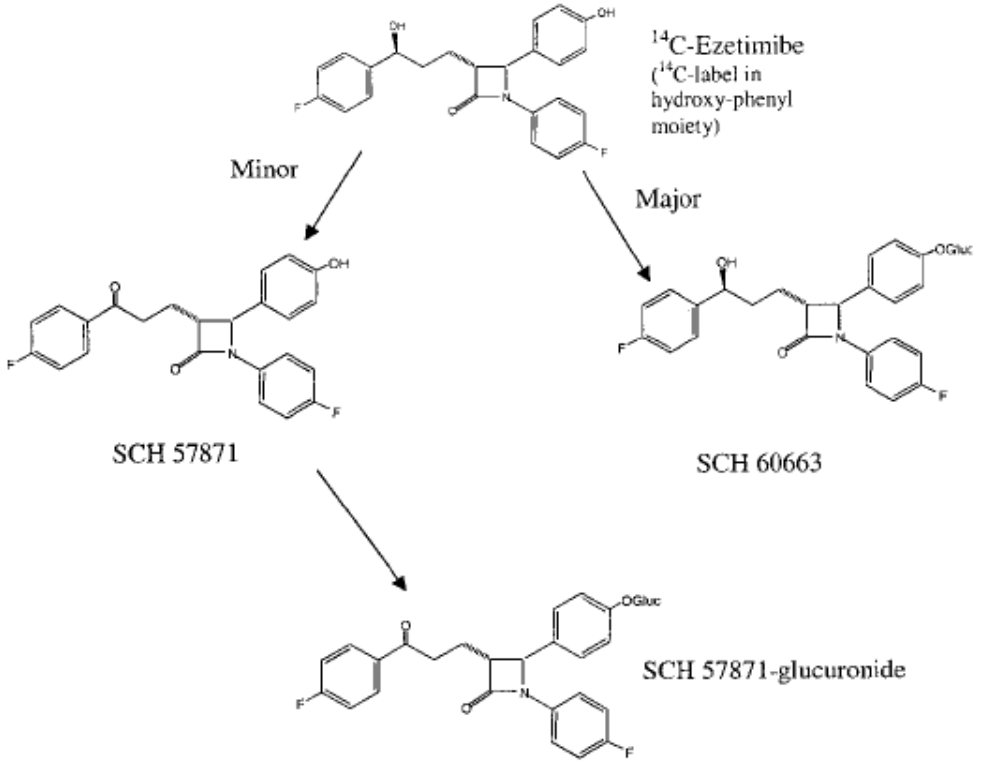
Ezetimibe and beta lactam-type hypersensitivity Chemistry

- Beta lactam antibiotics trigger allergic response by metabolic opening of the beta lactam ring & binding to proteins





- Beta lactam ring of ezetimibe is ***excreted intact*** by humans



Patrick et al., 2002

It’s all in the data…

- ✓ Dedicated manufacturing is used to protect patients against carry- over of highly sensitizing compounds into other drugs
- ✓ An extensive body of data shows ezetimibe has an exceedingly low potential for hypersensitivity and no potential for beta lactam-type allergic response
- ✓ Data suggests dedicated manufacturing for ezetimibe due to beta lactam concerns isn’t warranted and potentially reduces availability of a key medicine
  - ✓ Difficult situation since draft guidance requires otherwise
  - ✓ How can this be resolved for patients?

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Backup Slides

Highly Sensitizing definition

- "GUIDELINE ON SETTING HEALTH BASED EXPOSURE LIMITS FOR USE IN RISK IDENTIFICATION IN THE MANUFACTURE OF DIFFERENT MEDICINAL PRODUCTS IN SHARED FACILITIES" (PIC/S 1Jul 2018) https://picscheme.org/docview/2467
- 5.2 Active substances with a highly sensitising potential
  - 5.2.1 Drug-induced immune-mediated hypersensitivity reactions may develop in sensitive individuals. The observed reactions may range from mild cases of contact sensitisation to potentially lethal anaphylactic reactions.
  - 5.2.2 As outlined in Chapter 3 paragraph 3.6 of the GMP guideline, dedicated facilities are required for manufacturing active substances and medicinal products with a high sensitising potential for which scientific data does not support an acceptable level of exposure or the risk associated with handling the product at the facility cannot be adequately controlled by organisational or technical measures. Classification of an active substance or medicinal product with a high sensitising potential should consider whether the substance shows a high frequency of sensitising occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal data or other validated tests. Severity of these reactions should also be considered and should be included in a weight of evidence assessment